A Framework for Simplification of Clinical Trials in Regulated Medical Devices

Medical Device Innovation Consortium (MDIC)
Clinical Trial Innovation and Reformation (CTIR) Committee

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The Medical Device Innovation Consortium (MDIC) is the first-ever public-private partnership created with the sole objective of advancing the regulatory science around the development and assessment of medical devices. Members of MDIC share a vision of providing U.S. citizens with timely access to high-quality, safe, and effective medical devices without unnecessary delay.

**Background on the MDIC CTIR Committee**

The MDIC Clinical Trial Innovation & Reform Steering Committee (CTIR Committee) was established to address issues of growing inefficiencies in the clinical trial ecosystem for the medical device industry. MDIC aims to improve the medical device clinical trial enterprise, driving a coordinated effort to fundamentally change how medical research is conducted. Clinical Trial Simplification is one of the projects the CTIR initiated to achieve their goal. The MDIC CTIR Committee comprises leaders from the medical device industry, Food & Drug Association (FDA), National Institutes of Health (NIH), patient groups, and academia.

**Problem Statement**

Presently, medical device companies following the FDA Pre-Market Approval (PMA) pathway employ increasingly complex clinical trial structures that are inefficient and burden the clinical research and regulatory evaluation processes. This growing burden contributes to excessive costs, and impedes the processes of new device approval and approval of new treatment indications of existing medical devices, therapies, and diagnostics. Ultimately, these burdens delay access of medical devices to patients and providers in the United States. The cause of the growing complexity and potential inefficiencies in medical device clinical trials is multifactorial, involving growing evidence demands and activities from all stakeholders, including industry, academia, payers, and the FDA.

The Center for Devices and Radiological Health (CDRH) considers strengthening the clinical trials enterprise a high priority and the promotion of clinical trial simplification a key principle. William Maisel, MD, MPH, Deputy Director for Science, Chief Scientist and Acting Director, Office of Device Evaluation, has indicated that by “simple,” CDRH means “efficient,” and there is opportunity to drive efficiency (defined as maintaining safety, quality, and efficacy) throughout the clinical trial process, including in design, execution, and analysis.¹

The clinical research community, through publications, workshops (e.g., Institute of Medicine [IOM], Clinical Trials Transformation Initiative [CTTI]), and other initiatives, has also recognized the problem of overly complicated and inefficient clinical trial structures and operations. The community has strongly recommended the simplification and increased efficiency of clinical trials.

**Background on the Problem Statement and Potential Approaches**

*Trials have grown in complexity with significant cost and time implications.*

The growth in complexity of clinical trials has been well characterized in the literature. Complexity can be quantified in numerous ways including the number of sites, geographies, eligibility criteria, patients, clinical procedures, and data points. One study
evaluating over 100 trial protocols reported that the median number of clinical trial procedures grew by 57% over a decade (non-device clinical trials). Approximately half (47.9%) of the clinical trial procedures in the pivotal trials supported what were determined as core endpoints (i.e., primary, key secondary, safety endpoints), while nearly 25% supported non-core endpoints (i.e., considered ancillary and exploratory endpoints). These non-core endpoints may directly contribute to inefficiency or “waste” from a cost, time, and focus standpoint. Alternatively stated, although the high amount of data collected may be used in tables, lists, and graphs, a significant portion of that data may not be needed for regulatory, reimbursement, or defined trial protocol reasons. On average, the study demonstrated that 18.5% of the total direct costs spent on all trial procedures were spent to support non-core endpoints. This burden has substantial implications considering the average total direct costs supporting all trial procedures was reported to be over $9.0 million in this study.2

There is an inverse relationship between the complexity in a protocol and performance and quality of the clinical trial. An increased burden in data monitoring is a direct result of more data collection and complexity of trials. It has been reported that nearly 90% of non-core data points are verified by site monitors, adding substantial time and costs to the study even though the data are not utilized to support key objectives of the program (e.g., regulatory approval decision making, reimbursement). Verification of non-core data not only adds to monitoring costs, but also adds study costs through the data quality verification process. Data quality verification is the resulting verification processes from data queries, which result from inherent mistakes or data clarifications identified during monitoring. For example, publications have shown that every data point quality check (QC) results in approximately 1 hour of additional time between site and sponsor for verification, communication, database correction, etc. With increased data collection volume comes increased QCs at a cost of approximately 150 Euro each, yet up to 99.6% of queries have been found to be unrelated to a trial’s primary endpoint results. Given that thousands of queries are typically generated in a study, it is intuitive to extrapolate that costs can be reduced through focused data collection which addresses core study endpoints. In pharmaceutical trials, Eisenstein showed that greater than 40% of trial costs can be reduced through simplified trial management components (defined as reduced CRF [Case Report Form] pages, monitoring visits, and the reductions in site payments corresponding to these activities).5 While further research is needed to determine how savings from medical device studies compare to pharmaceutical studies, due to trial management similarities, it is reasonable to infer similar savings are achievable for medical devices.

More complex protocols can expand study times and contribute to slow recruitment, poor retention, and an increase in the number of protocol amendments. One review of over 3,000 studies (non-device) reported that nearly 60% of the protocols resulted in one or more protocol amendments, adding time and cost to the study. One-third of the overall amendment changes were rated by the sponsors to be somewhat or completely avoidable. Reasons for these changes included design flaws, errors, and recruitment challenges. There is considerable room for simplification in clinical trial design and driving efficiencies in processes to minimize issues that lead to protocol amendments.6,7

While there is opportunity within the literature for additional study on the hypothesized growth in complexity of medical device clinical trials, there is also widespread recognition of needed medical device clinical trial simplification as demonstrated through public comments, guidance, and workshop reports from FDA, industry, and the research
community. Many of the key complexity indicators quantified in the literature related to pharmaceutical trials are universal to general clinical trial processes, and therefore relevant to medical device trials.

**What drives the growing complexity in clinical trials?**

Clinical trials designed for medical device regulatory approval are intended to produce valid scientific evidence to demonstrate a reasonable assurance of safety and effectiveness for the intended uses and conditions of use. Additionally, sponsors must consider designing trials to produce evidence required for payers, clinicians, and other important stakeholders. In general, a core data set for a trial typically includes those endpoints and data supporting regulatory approval decision making, reimbursement, and other critical objectives. However, there is a wide variety of opinions on what may be defined as “critical,” both within and external to the study sponsor.

Sponsors collect data to guide current and future product development, respond to ongoing regulatory and ethical committee requests, expand publications, and respond to a variety of other internal and external stakeholders as the protocol development and regulatory approval process evolves over time. Sponsors aim to develop all the evidence needed to maximize the probability that their device will be approved, paid for by insurance, and accepted and used by healthcare practitioners. One report proposes sponsors are engaging in a growing pattern of “defensive data collection,” the practice of incorporating ever-expanding data elements into a protocol in anticipation that a stakeholder may ask for the data after study completion. This pattern of growing procedures and data collection beyond the core data set increases burden on sites, indirect costs, and burden on trial participants.

Success with past trial designs commonly drives future templates and standard processes and procedures. Both sponsors and FDA reference historical trials with learnings related to successes and failures, including an identification of core data sets considered critical for regulatory decision making. While this approach is sound from a learning standard and intentions are good, the process itself may lead to inadvertent inclusion of data, procedures, and approaches that are not necessarily critical to the immediate trial and its objectives.

It is critical for sponsors to document clear and convincing rationale for study designs and core data sets through the negotiation process with FDA and other stakeholders (internal and external). This includes articulating where other data may have been considered, but determined not to be critical to the core data set for the identified objectives.

**An imperative for larger trials in the simplification process.**

Medical research aims to ask important questions and provide reliable answers through clinical trials. Randomized clinical trials (RCTs) have long been the gold standard for determining the safety and efficacy of medical therapies and other interventions that will improve health and healthcare. Increasingly, the regulatory and reimbursement environment is demanding more than just RCTs to demonstrate safe and effective use of medical devices and diagnostics. There is a growing need for economic data in conjunction with clinical data. Thus requirements for large observational trials in conjunction with randomized controlled trials are becoming more common to meet the
It has been reported that many regulated trials are not of an adequate size to reliably evaluate the risk-benefit in the regulatory process. A key measure of efficiency in a clinical trial or clinical trial enterprise should include the ability to use evidence to make meaningful clinical decisions. A study of post-approval studies required by FDA in high-risk medical devices reported that small sample sizes in these regulated studies may hinder the results from being clinically useful. In addition, the populations being studied today have much lower incidence rates of disease or therapy, requiring larger sample sizes to show meaningful differences and affect potential medical management.

The call from the clinical research community to simplify the clinical research process includes consideration of large simple trial (LST) and pragmatic trial designs, whenever possible. The success of simple and inexpensive randomized controlled clinical trials performed on scalable observational research platforms (e.g., the Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia [TASTE] Trial) has been recognized as a desirable future platform for many clinical trials. One of the clinical research community initiatives to date has primarily focused on drug clinical trials, though there are device examples (e.g., the Dual Antiplatelet Therapy [DAPT] Study). There is a need to increase our understanding of when and how the LST design may best apply in regulated medical device trials.

It is clear that medical devices differ from pharmaceuticals, including by mechanism of action. Devices have a primary mechanism of action that is typically physical and focused in nature. Further, as devices evolve, they collect more diagnostic information, leveraging increasingly robust physiologic sensors, which differentiates device clinical trial design from pharmaceutical trial design. Device “use” is a critical factor in medical device therapies (e.g., learning curve in device use, implant, or procedure technique evolution and variability). Many devices are developed and intended for use in a narrow patient population. Early feasibility studies (EFS) are small studies that may be conducted with medical devices to collect early safety and effectiveness data and/or to better understand device use aspects important in the design of a scientifically sound pivotal study. While some differences between device and drug development necessarily lead to differences between trial designs, design similarities do exist. While generally there are legitimate reasons why device trials may be smaller than pharmaceutical trials, many LST principles may still be applied to device trials to drive efficiencies.

The design of all trials should include consideration of whether the sample size is “large enough” to produce results that are valid, generalizable to a broad target population, and allow for adequate evaluation of a risk-benefit balance. Caution is warranted to ensure any focus on creation of larger trials does not establish a trend towards large, complex trials or serve as an automatic response to criticisms above. Clearly, the size of a trial should be thoughtfully determined by key objectives and methodological and statistical considerations. This is key to the establishment of a clinical trial enterprise that will drive
efficiencies and maximize impact of fixed research dollars to improve health and healthcare.

**Potential approaches for simplification in clinical trial design and operations.**

The literature reports a variety of approaches for the clinical trial enterprise to consider in driving simplification and efficiency, including in time, cost, and quality. Approaches and opportunities can be categorized under areas of design and operations of clinical trials throughout the regulatory approval process.

### Design

Innovation in design of clinical trials continues to evolve and FDA has been a strong partner in the promotion of new methods through its participation in workshops and guidance. The designs of large simple trials (LSTs) and pragmatic trials provide significant efficiency opportunity. LSTs are characterized by simple randomization, broad eligibility criteria to promote generalizability, sample sizes large enough to detect small or moderate effects sizes, and outcomes of meaningful clinical importance that can be efficiently and effectively captured.

Pragmatic trial designs embed clinical research protocols in the clinical care setting and systems at the point of care. This is the concept of designing the clinical trial to conform as closely as is reasonable to standard of care (SOC). The less a protocol varies from SOC, the more likely it is that the site and the patient will be compliant with the protocol and the more likely it is that correct data will be collected. When extraordinary tests are required, or when a patient is asked to come back more frequently and at intervals not typically required for treatment and follow-up, the more likely it is that the patient will either decide not to participate in the study, or will not comply with the follow-up schedule. In addition, this only adds burden to the sites’ already busy schedules and increases the likelihood of missing data, which in turn increases the need for queries and further annoyance of the stressed research coordinators.

FDA has provided guidance on the use of the adaptive trial design in medical device trials and continues to promote increased application in regulatory submissions. However, application and use of this design has not been widely adopted for regulated medical device trials. Adaptive trial design has the potential to drive efficiency as it allows pre-specified interim evaluations of the accruing data while maintaining the scientific integrity and validity of the study. An example may be an interim analysis that results in stopping the trial early for effectiveness or futility, based on pre-defined criteria. Stopping the trial early based on success criteria can clearly accelerate the time to getting a new therapy to patients and save significant money that could be shifted to research in another area. Similarly, the trial may be stopped early for futility, and while this is not the desired outcome, stopping early with confidence minimizes continued exposure to patients and again, allows a company to manage distribution of fixed research dollars. The adaptive design may also be used to support the balance of clinical data collection requirements across the pre- and post-market settings. For example, a study designed with a pre-planned interim analysis may demonstrate success to support the marketing application with planned
continuation and long-term follow-up of the study subjects as a post-approval requirement.3,11

Other approaches, such as Bayesian designs or computer modeling and simulation methods, continue to evolve in application and may also be considered to provide opportunities for sponsors to drive efficiencies in clinical trial design.

Operations
Sponsor processes and procedures for the design and execution of clinical trials provide a foundation for driving simplification and efficiencies through the design, execution, and management of trials.12 Standardized procedures for clinical trial design and approval should establish clear cross-functional roles, responsibilities, and accountabilities. Processes should incorporate oversight management throughout the clinical trial lifecycle and include triggers for consideration and approval of protocol amendments. This includes processes and documentation requirements in the negotiation and finalization of design and core data sets with FDA and other stakeholders.

Focused data collection is a key simplification principle for transformation in the clinical trials process. There are broad recommendations for clinical trials to streamline and limit data collection to a critical data set (i.e., core data), most often defined as the sufficient data required to support regulatory decision-making process and other critical objectives (e.g., reimbursement, scientific publications). It will be essential for sponsors, regulators (e.g., FDA reviewers), and the scientific and healthcare community to align behind streamlined data sets throughout the lifecycle of a clinical program, pre-approval and post-approval.2,7,12

Processes in design, control, and ongoing change management of the protocol, case report forms (CRFs), databases, monitoring plans, and other components of the clinical trial infrastructure must support focus on the defined critical data set. Increased efficiency may be driven through use of standards across all of these areas (e.g., data fields, CRFs, report templates, database development). Additional data standard opportunities (e.g., CDISC), including creating core libraries, could streamline data collection elements, thereby reducing database development and subsequent submission timelines. Approaches to drive efficiencies should be considered for implications within a specific trial and impact across trials.

Site management is an area with good opportunity for finding efficiency and optimizing study performance (e.g., time to complete enrollment, quality errors, retention). Site feasibility and selection processes should ensure the “right trials” are matched with the “right sites,” based on experience, resources, infrastructure, target patient population, etc. The goal is to select sites that will efficiently contribute quality data to the study in a timely fashion. Repeat selection and ongoing support for top-performing sites allows these sites to refine tools and optimize systems (e.g., validated instruments aligned with clinical care, electronic data collection [EDC], automating data integration from existing systems) increasing their future efficiencies and sponsor return-on-investment (ROI).9,12
Novel data acquisition methods continue to hold promise for efficiencies in clinical trials. High on the list is direct transfer of data from electronic health records (EHR) as expanded on below. It also includes use of mobile and online technologies for collection of patient-reported data and conduct of the informed consent process. Additionally, the use of telemedicine in research for the conduct of virtual study visits is an exciting application to consider. These new technologies may minimize potential for lost data and participant drop-out by engaging patients directly and remotely.

Finally, data monitoring innovations that decrease the burden of data monitoring and reduce costly onsite visits may be recognized without decreasing the scientific validity of the study or impacting patient safety. For example, FDA supports the electronic transfer of data elements directly from an EHR to the research electronic case report form (eCRF) to reduce potential for transcription errors. The EHR is the source record in this case and central monitoring of the system and data transfer processes may be conducted to support appropriate security and integrity of the research data transfer. This does not necessarily eliminate onsite visits, but provides significant opportunity to reduce the burden. Techniques and approaches continue to evolve and be promoted by FDA in this area (e.g., risk-based monitoring), though application in medical device trials has not been widely reported.

Opportunity to Address the Problem for Regulated Medical Devices

As presented in the background above, there is significant opportunity to apply “simple” or “efficient” principles in the design and execution of all medical device clinical trials to maximize potential for reducing costs and time, and to produce evidence that is meaningful in both regulatory and clinical decision making, though it is not compatible with the present state of the medical device clinical trial enterprise. The MDIC has developed a framework to further evaluate and address the problem of growing complexity in clinical trials and opportunities for change specific to regulated medical devices. Although this Framework specifically addresses the PMA in the United States, it is worth noting that solutions from MDIC may have impact on U.S. post-market studies, research studies, and post-approval studies, and eventually may impact global trial design.

MDIC Framework for Simplification of Clinical Trials in Regulated Medical Devices

Overall, the MDIC Framework for Simplification of Clinical Trials in Regulated Medical Devices intends to advance multi-stakeholder alignment for a paradigm shift in medical research through the simplification of clinical trials in regulated medical devices.

The main objective is to advance health and healthcare by bringing important medical innovation forward through a more robust and efficient (cost, time, quality) clinical trial enterprise. The approaches are aimed at maximizing potential for complete and reliable data sets in clinical trials to support key decision-making processes without excessive data collection, while maintaining safety and increasing quality.

MDIC aims to better understand the need for and barriers to simplification of regulated medical device clinical trials and explore the status of the high complexity of regulated medical device clinical trials, to determine whether the problem statement is valid. If

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valid, the MDIC CTIR Steering Committee will explore causes, impact on the regulatory
process, patients, and healthcare economics, and propose remedies with associated
tools to simplify and drive efficiencies in regulated medical device clinical trials.

MDIC will propose a pathway to support industry in the transformation towards
simplification of all clinical trials as they drive efficiencies through design, operations,
and the regulatory process. The pathway will be presented in the form of a blueprint
(MDIC Blueprint for Clinical Trials Simplification) and an associated library of tools. The
library of tools will be established through industry sharing of best-practices and may
include whitepapers (e.g., risk-based monitoring approach), templates, and other
instruments.

In addition, MDIC will facilitate broad stakeholder engagement to develop a better
understanding of the roles and responsibilities of industry, academia, providers, payers,
patients, and the FDA in initiating and sustaining the paradigm shift required to drive
transformation. Learnings will inform the change management strategies required to
align incentives and alter the activities of all stakeholders. The MDIC fully understands
and respects the independent role of FDA and their policy processes, and aims to
provide objective data necessary for the FDA to react to and make independent
decisions.

Further, the project will provide demonstration metrics and evaluate the value of the
MDIC Blueprint for Clinical Trial Simplification by following and reporting on case studies
and clinical trial programs that implement principles of simplification through the
regulatory process and experience as it is gained with the new processes and
procedures. A strategy for change will be developed and include publications and other
timely dissemination of information for all key stakeholders.

**Framework for Clinical Trial Simplification in Regulated Medical Devices**
1. **Frame the opportunity related to medical devices.** MDIC will compile an overview and assessment on the rationale and proposed approaches for clinical trial simplification to provide insights on the hypothesized problem statement. The assessment will aim to understand the environment specifically as it relates to regulated medical devices, with comparisons and contrasts to and from drugs and other non-medical device products. This assessment will work to consider various trial types, including: interventional trials, post-approval studies, and observational registries. This will be conducted through review of peer-reviewed scientific literature, original reports, and other published writings. This activity will also provide information to ensure MDIC focuses project activity and minimizes the potential for duplication of efforts for all stakeholders.

2. **Data analysis documenting burden related to medical devices.** MDIC will develop a focused survey of industry sponsors to test whether the concepts of complex or overly complicated clinical trials are viewed as a problem for regulated medical device clinical trials, and if so, explore barriers to and opportunities for clinical trial simplification. Additionally, analysis will include using data from selected clinical trials under PMA and some 510(k) pathways. MDIC will develop a method and explore what set of key data were critical and necessary for product approval and/or indication expansion (using defined criteria for assessment) and compare them with the data sets included in the CRFs. This analysis would identify opportunities to maximize time and effort, and confirm previous reports drawn from non-medical device analyses and publications. Past FDA clinical trials will also be assessed for level of adjunctive trial activity, including trial management components (e.g., data monitoring, database development), usage and degree of core laboratories, clinical adjudication committees, Institutional Review Board (IRB) timelines, Data Safety Monitoring Board (DSMB) employment, etc. The data collected may then be analyzed to show the level of variance among trials, and methods devised and performed to understand time impact, costs, and the risk-benefit of data collection and trial adjunctive activity.

3. **Industry pathway and tools for simplification of clinical trials.** MDIC will develop a blueprint or guide (MDIC Blueprint for Clinical Trial Simplification), informed by the learnings from above projects, to address methods and considerations for simplification and efficiency specific to the design and operations of regulated medical device clinical trials. The Blueprint will include an associated library of tools, best-practices, and device-specific case studies. Tools and best practices may include approaches for leaning data elements in CRFs, applying risk-based monitoring in medical device trials, implementing data standards (e.g., CDASH), etc.

4. **Regulatory engagement.** MDIC will continue to partner with FDA in the establishment of a framework for clinical trial simplification in regulated medical devices that includes considerations for navigating the regulatory process to ensure a clear pathway for sponsors and for FDA to appropriately implement the Blueprint for Clinical Trial Simplification and tools with confidence. Additionally, the MDIC will develop a plan and methods for engaging independent expert panels (e.g., academics, healthcare practitioners) to develop consensus statements defining critical data sets sufficient to support regulatory approval decision making for key target therapies (number and targets to be...
determined). The consensus statement(s) may be published in the peer-reviewed scientific literature and would be intended to serve as unbiased references for sponsors and regulators (e.g., FDA reviewer) to use in the design and regulatory approval process for clinical trials as they strive to reduce the overall complexity of the clinical trial enterprise.

5. **Value demonstration of the MDIC Blueprint for Clinical Trial Simplification and tools.** IDE submissions that implement clinical trial simplification principles and the MDIC Blueprint will be tracked to understand and report on their value. The emphasis of the tracking will be to explore and report the strengths, weaknesses, and risks of clinical trial simplification for regulated medical devices, in order to build a strong foundation for change. Industry members and FDA will partner through MDIC to develop a plan with methods for tracking and measuring metrics, and processes to ensure both appropriate protection of confidential and competitive information, and independence of FDA in the regulatory decision-making process.

6. **Change management.** MDIC will develop an implementation strategy that provides broad communication and employs the tools of change as the above projects provide critical results and information. Communications will include publication through the MDIC website, peer-reviewed journals where applicable, and workshops, seminars, and public discussions. It will be essential to develop a strategy that ensures timely dissemination of information and appropriate communication for all key stakeholder groups.
References

1. Medical Device Innovation Consortium (MDIC) Clinical Trial Innovation and Reform Workshop: Removing the barriers to improving efficiency and effectiveness of medical device clinical trials – April 29, 2015.


