Joining Preclinical and Clinical Development

**Executive Summary**
When a medical device company uses NAMSA for both preclinical and clinical programs, as much as 6 months can be cut from the product development timeline. For the average 510(k) device with a 60-month development cycle, that could equate to a 10% reduction in total development time. For a product with annual revenues of $100 million, that can translate to a gain of $50 million in revenue. For smaller companies and start-ups, that means 6 months less cash burn before revenue starts to flow.

**Introduction: The MRO® Approach**
New medical devices are being developed to save lives, treat disease and injury, and improve the quality of life for patients around the world. The pathway from ideation to widespread patient use is highly regulated, complicated, time-consuming, and expensive. It involves many steps (Figure 1), each requiring specialized knowledge and expertise. Speeding up this development pathway has a great number of potential benefits:

- Patients and physicians gain access to breakthrough medical devices in a more timely manner
- Financial returns are generated sooner
- Development costs begin to be paid back more quickly
- Profits accumulate more quickly so they can be reinvested in more new products

Up to now, most timeline reduction strategies have focused on making individual components of the development cycle more efficient; for example, shaving a few days from a test turnaround time, parallel-pathing activities in a clinical trial, or rapid prototyping. These small efficiencies are not enough. If we are to make meaningful gains in reducing product development timelines, we must think and behave differently than we have in the past.

NAMSA, the medical research organization (MRO), believes there is additional success to be had by focusing on the intersection of adjacent development steps and by combining multiple steps or portions of product development into a more streamlined model. By offering unparalleled “end-to-end” services and employing cross-functional teams of experts, NAMSA has found unique ways to reduce the inefficiencies in and between development steps and significantly decrease the total time spent on new product development.

To achieve this, NAMSA has developed the MRO® Approach. In short, MRO refers to the unparalleled breadth of services NAMSA offers across the medical device product development cycle, utilizing an extensive team of experienced, dedicated, cross-functional staff who are committed to serving clients, and adept at finding ways to get products to market faster and with regulatory rigor.
Figure 1. Medical Device Development Pathway

- Ideation
  - Prototypes
  - Regulatory Assessment and Strategy Development (FDA, Notified Bodies, etc)
  - Clinical Strategy
  - Toxicology Risk Assessment
  - Non-GLP Cadaver Studies for form fit and function

- Proof of Concept
  - FDA Review of Clinical Plans
  - GLP In vivo Efficacy and Functional Performance Studies
  - Non-GLP In vivo Efficacy and Functional Studies
  - Biocompatibility

- Preclinical Development
  - Clinical Study Design Plans
  - Materials Characterization & Analytical Chemistry

- Clinical
  - Regulatory Submission Assistance; 510(k), PMA, CE Mark, etc (FDA, Notified Bodies, etc)
  - GLP Toxicology Risk Assessment
  - GLP In vivo Efficacy and Functional Performance Studies
  - Materials Characterization & Analytical Chemistry

- Regulatory Submission
  - FDA Panel Meetings
  - Biostatistics (Strategy and Execution)
  - Cleaning Validation

- Commercialization
  - KOL & Client Publication Support
  - Advisory Committee Support
  - Pre-submission Documents and Meetings

- Post Approval
  - FDA Inspection Preparation
  - Sales Training
  - Physician Training
  - Reimbursement Strategy Development
  - Reimbursement
  - Lot Release Testing
  - Manufacturing
  - Shelf Life & Accelerated Aging Tests
  - Post Market Surveillance (Clinical Trials)/MDR Reporting
  - Clinical Trials/Clinical Support (First in man, pilot, pivotal studies)
  - Quality System Regulation Support (QSR)
  - Quality System Audits
One area where NAMSA has found it can help clients significantly reduce medical device development timelines is in combined efforts across preclinical (efficacy, functional performance studies, etc.) and clinical programs. When NAMSA is hired to manage both of these programs for a particular product, key members of NAMSA’s clinical and regulatory teams are included in the development and conduct of the preclinical program. Doing so enables the clinical program to get started earlier and be managed more efficiently, and can cut the overall product development timeline by 4 to 6 months.

**Time to Market**

Reducing time to market has long been a goal in the medical device industry. For start-up companies, total product development time for their first product to either regulatory approval or acquisition is directly proportional to the amount of cash they will burn. The faster they can get to market, the less cash will be required—which translates into fewer rounds of funding and hence, less dilution for founders and early investors. For established medical device firms, new products can be significant growth drivers, making new product development timelines critical to meeting financial expectations, which is important for stock market expectations, departmental/divisional success, and personal career growth.

**Product Development Timelines**

Unfortunately, instead of getting faster at developing new products, the industry at large has gotten slower. In fact, getting new products to market seems to be getting harder and taking longer than ever—and the trends do not appear to be changing. From 2007 to 2013, the median time it took for a start-up company to go from company inception to their first 510(k) went from 3.5 years to 5.2 years (Figure 2).¹ The average product development costs to reach approval have been estimated to be between $31 million (low- to moderate-risk product) and $94 million (higher-risk product).²

![Figure 2. Average and Median Time to First 510(k) Clearance, 2007-2013*](image)

* N=491 510(k)s, of which 92% are for Class II devices. Excludes outliers of <1 year and >16 years.

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Impact of FDA

From 2000 to 2010, average FDA decision times for 510(k) submissions increased 60%, from 96 days to 154 days (Figure 3). This increase has been partially driven by the significant increase in FDA Additional Information (AI) requests (Figure 4).

Figure 3. Average Time to FDA 510(k) Decision

FDA has made a concerted effort to reduce decision times in recent years. While final data for 2013 and 2014 will not be available for some time, the current trend is encouraging as indicated by the most recent FDA report (April 28, 2015). However, other factors working against such a trend (increases in additional information requests, number of pages per submission, testing requirements, etc.; see below) make one wonder if we can ever get back to decision times under 100 days.

Figure 4. Percent of 510(k)s with Additional Information (AI) Request at First FDA Review

2013 data are for first 3 months.
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At the same time, increasingly stringent regulatory requirements and agency policies have caused a significant increase in the amount of testing, the number and size of preclinical evaluations, and the likelihood of a clinical evaluation requirement in 510(k) submissions. These factors are reflected in the ballooning growth in size of the average 510(k) submission (Figure 5).5

Figure 5. Average No. of Pages in a 510(k) Submission (1983-2008)5

PMA approvals for higher-risk devices have become even more burdensome. The average cost to put a PMA product on the market is about $94 million, with an average of 4.5 years (54 months) from first contact with FDA to device approval.2

Clearly, strategies to reduce development times while maintaining product quality and regulatory compliance rigor offer important benefits for developers of medical technologies.

Some Advances

A handful of successful strategies are enabling device makers to get to market a bit sooner. At the earliest stages, advances like concurrent engineering, rapid iterative prototyping, and 3D printing allow companies to get to a “clinical unit”—a device design with which the company will perform its preclinical, clinical, and regulatory programs—more quickly.

On the regulatory front, FDA has encouraged greater use of pre-submission and other meetings to help companies get a better sense of what FDA will require for a specific product. The idea is that, if the company believes they know what FDA wants to see in their submission, they will be better able to tailor the development program to include the required data. In theory, this should allow the company to avoid the time and expense of unnecessary studies prior to submission, and reduce or eliminate the time and cost of additional testing or studies after submission.

On the clinical front, replacement of paper forms with electronic document and database systems, coupled with intelligent statistical programming, has shortened the time it takes to clean data and lock the database; resulting in a
reduction in time from the last patient visit to completion and submission of the trial study report. The more recent introduction of an Electronic Trial Master File (eTMF) system has the potential to improve site start-up times, which would reduce the overall clinical trial timeline while also offering higher quality and better regulatory compliance. Perhaps the biggest potential impact on clinical trial costs is the (yet to catch fire) implementation of a risk-based approach to monitoring where sponsors can target their on-site monitoring visits where/when needed, thus allowing them to focus their dollars on other areas of the product development cycle.

However, there have been few other timesaving innovations associated with preclinical or clinical programs, and almost none that have addressed the timesaving opportunities inherent in linking preclinical and clinical development. In fact, that is precisely where internal organization and traditional practice have tended to maintain the status quo and regulatory requirements have tended to increase the timeline most.

**Standard Product Development Practice**

Medical device product development is complex and requires a great deal of specialized knowledge at each step of the process (see Figure 1). In larger medical device companies, most of the new product development work is still conducted in-house, with only the most standard or routine tests or tasks being outsourced. The product development activities are often “silod” into specialty departments (preclinical, regulatory, data management, clinical affairs, etc.), which are then assigned their specific portions of many different product development initiatives. Each department’s portion of product development (and the development timeline) for each new product usually has clearly defined boundaries and goals. Everything these individual departments do is focused on their specific portion of the development cycle. While they work with others in a more global “development team,” each department is somewhat an island without real investment in, control of, or impact on the other departments’ projects, timelines, practices, or procedures. They are the subject matter experts in their specific area of responsibility, and are expected to be as efficient and effective as possible with their specific portion of the development program.
Smaller companies have fewer people and almost by definition have less development “power” than larger companies. They typically supplement their internal resources with outsourced help from Contract Research Organizations (CROs) as a matter of necessity. Since they don’t have enough people in their internal departments to handle the work, they effectively extend their internal departments by adding external short-term expertise and labor from the CRO. The result is that a single small medical device company can be working with many different specialty CROs on the same development program. By the time they are done, they often will have contracted with a regulatory consultant, a preclinical lab, an analytical laboratory, a biocompatibility lab, a microbiology lab, a consultant for cleaning validation, a packaging consultant, a packaging integrity lab, a data management CRO, a clinical CRO, a reimbursement consultant, and so on. Such an arrangement is inherently inefficient; and tracking, consolidating, and managing the quality of these disparate contributions can be more than a full-time job for several individuals in an environment where almost everyone is already overburdened.

For both large and small medical device companies, the overall idea is that, if the entire development program has someone looking after it, and if the hand-offs between departments or CROs are well managed, the entire development program will flow as smoothly and as quickly as it can. While this can work, it inherently misses significant time savings and synergies.

The Preclinical/Clinical Intersection

One particular place NAMSA has found to significantly reduce time in the development cycle is the intersection between preclinical and clinical development.

The preclinical and clinical development of most devices are almost always handled by different departments or groups that have their own sets of specialized knowledge and experience. When outsourced, the studies are nearly always subcontracted to different CROs. This makes a certain kind of sense: one group deals with non-human test models, and one deals with humans; one deals with IACUCs and GLPs, and the other with IRBs and GCPs. The result of using separate CROs is that very little, if any, overlap or efficiencies are gained in the preclinical/clinical segment of the timeline.

Employing the MRO model, NAMSA has services spanning the product development lifecycle, including preclinical and clinical development services. When a client uses NAMSA for both the preclinical and clinical portions of their development, NAMSA can shave as much as 6 months from the timeline.
So, how is this accomplished?

The MRO Philosophy: Integrated, Cross-Functional Teamwork

A core philosophy of the MRO concept is integrated, cross-functional teams that span adjacent portions of the development continuum. When NAMSA is able to conduct both the preclinical and clinical programs, NAMSA assembles a multidisciplinary team including preclinical, clinical, and regulatory staff, as well as representation from the sponsor and sponsor selected key opinion leading physicians. This team works at both the individual project level and at the larger program level to coordinate all of the activities across the preclinical and clinical programs. They will create a fully integrated program designed to avoid or minimize time gaps between sequential tasks, and coordinate resources for performing tasks that can be done in parallel.

Vendor Identification and Qualification

There are a number of other places where time savings are gained. The first is in the vendor identification, selection, and qualification process. It typically takes a sponsor 4-8 weeks to identify and select the final vendor for a preclinical project. This includes:

- Identifying potential labs that are qualified to do the work
- Having preliminary conversations with each of the labs’ sales and technical staff
- Preparing the RFP or project details
- Requesting and receiving back quotes from the selected labs
- Evaluating each of the quotes
- A bit of back and forth with the finalists to ensure understanding of the project details and the quote
- Selecting the best partner
- Conducting a paper audit and often an on-site audit

This process can be shortened to 3 to 4 weeks if the sponsor has a preapproved list of already audited labs or has experience with certain lab(s) they have chosen to give most of their work. In those cases, the sponsor still must prepare the project details such that the lab can prepare a quote. The lab typically will want a conversation with the sponsor team so that there is good understanding of the project scope. The quote is then prepared by the lab, and reviewed and discussed with the sponsor.

When a sponsor uses one vendor for the preclinical program and another vendor for the clinical program, it means they need to go through two different vendor selection processes. When NAMSA is selected up front to conduct both programs, it may take another week to make the final CRO selection, but the total vendor selection process is greatly condensed. This can result in a net savings of 5+ weeks in the timeline if it is on the critical path, and still eliminates a great deal of work downstream if it is not.
CRO Contracts
CRO contracts are another area where a bit of time can be shaved from the timeline. Getting a contract in place with a CRO typically takes 3 to 4 weeks of elapsed time. If there are two vendors with two contracts being negotiated at separate times, the sponsor can expect it to take 3 to 4 weeks each, with a combined hit to the timeline of 6 to 8 weeks. Again, the process can be shortened if the sponsor is working with CROs with whom they already have Master Service Agreements (MSAs) in place. In those cases, work orders under the MSAs are typically completed. Work orders move much faster than a complete contract and can usually be completed from start to finish in 2 to 3 weeks.

When NAMSA is selected for both programs, only one MSA will be negotiated, and all work for both programs will be conducted under work orders, saving a total of 3 to 4 weeks from the timeline if the clinical contract ends up on the critical path. And if not, once again, significant work is still eliminated downstream.

Preclinical Study Design/Project Planning
Once the sponsor has chosen the preclinical CRO, the CRO will begin to plan and prepare for the preclinical study(s). This includes:

- Institutional Animal Care and Use Committee (IACUC) review and approval
- Protocol and case report form development
- Test model acquisition
- Procedure scheduling

When NAMSA conducts both the preclinical and clinical programs, key members of the clinical team will take part in many portions of the planning and execution of the preclinical studies. They will provide input on all facets of the preclinical protocol and study documentation (Case Report Forms, Adverse Event Forms, Protocol Deviation Forms, etc.). They will work with the preclinical team veterinarians and physicians in the development of physician training programs. The relationships established during the preclinical evaluation serve to enhance the collaboration of the clinical team with physician investigators in the subsequent clinical phases. In addition, by teaming with preclinical investigators, these experts are available for technical support throughout the clinical evaluation and regulatory review phases.

Expertise leveraged from the clinical research and regulatory team improves the quality of preclinical protocol design and quality of the preclinical data collection. It also may allow resolution of important clinical or regulatory questions during the preclinical phase.

In addition to time savings, this linkage offers rigor and risk reduction to the clinical program. All of the lessons and knowledge acquired in the preclinical process can be better leveraged to reduce risks in the clinical evaluation phase. This is achieved through the teamwork of the multifunctional team.
The continuous knowledge sharing achieved through the preclinical process, and the continuous scientific support this team has contributed, can continue throughout the clinical evaluation phase. Lessons learned, data collection and piloting case report forms, data sharing, and expert iterations all serve to shorten the interval to clinical initiation and bolster the value of a company’s investment in data.

**Preclinical Database**

Often, preclinical studies use very rudimentary data storage solutions. Preclinical data may be stored in a lab notebook, raw data sheets, cardboard boxes, and/or in digital files in office software or monitoring devices. The rationale used to justify this simple approach is saving investment during the early development phases. However, data management by these techniques is quite inefficient. Reporting for management meetings, publications, and regulatory submission is quite laborious under this system, requiring manual efforts and an increased potential for errors.

NAMSA realizes preclinical data may be utilized more fully and efficiently when stored and accessed through database solutions. In the preclinical/clinical model, case report forms and adverse event forms are piloted with early database construction in preclinical studies. The increased preclinical database investment is repaid in reduced clinical trial database construction costs.

Future supplemental products and generations can also leverage existing data management tools, including the database and case report forms. Common data fields across preclinical and clinical studies offer improved access to data for comparison, research questions, publications, and regulatory submissions.

The preclinical study database also provides the sponsor, who oftentimes is based in another city or country, with real-time visibility to their study data. Finally, the preclinical database can foster knowledge sharing between the multifunctional team members and other current and future sponsor team members.

“Adverse event handling mechanisms developed and piloted in the preclinical study database can help with the clinical study design.”
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Preclinical Program Execution
When NAMSA conducts both the preclinical and clinical programs, key members of the NAMSA clinical team will observe the procedures and become familiar with the device—its complexities, tendencies, and behavior—before, during, and after surgery. Key benefits of this early interaction and collaboration include:

- The opportunity to interface with physician medical advisors and future principal investigators
- Increased collaboration and teamwork between the institution, sponsor, and clinical trial management team
- A better understanding of the way the device performs; the ability to actually see the device in action, and interact with the surgeons and study directors before and after the procedures
- The opportunity to look for potential issues related to the clinical program which may be identified in the preclinical program — and proactively devise solutions
- Piloting of tools such as informational brochures, training, case report forms, and actual protocol methodology
- A better understanding of necessary enhancements to written direction, data collection, and documentation
- The ability to better anticipate and plan for the coming clinical trial experience, especially as it relates to adverse events and device efficacy results and reporting; in essence, the ability to use the preclinical experiences and observations to serve as a “dry run” for the clinical protocol
- Early understanding of potential physician user issues, and better understanding of how to train physicians for the clinical study

Transition from Preclinical to Clinical
Normally, once a preclinical CRO or team completes or is close to completing the preclinical phase of development, a separate clinical team or clinical CRO will be selected to move the program into the clinical phase. The clinical CRO is generally unfamiliar with the product and with the studies that have come before. Training of the clinical team on the product, regulatory plan, preclinical performance, and so on is typically completed by the sponsor, and can take anywhere from 2 to 3 months. This is a time-consuming effort for the sponsor, but is critical for the success of the clinical program.

When NAMSA conducts both the preclinical and clinical programs, there is no need for the sponsor to train the NAMSA clinical team. They will have been intimately involved with the device long before the clinical studies start, and will already be trained. Furthermore, because they will have been working alongside the preclinical team, the clinical team will be able to start many of the planning and design phases of the clinical studies earlier than what would have otherwise been possible. This results in a significant reduction in workload on the sponsor, and enables the NAMSA clinical team to move immediately into the clinical study phase. Total timeline savings here varies, but could be expected to be, at minimum, 2 months.
Clinical Study Design/Project Planning

When NAMSA performs both the preclinical and clinical programs, and are tasked with the protocol development, the knowledge gained from the preclinical program allows us to complete the protocol development in roughly 6 weeks from completion of the preclinical study instead of the typical 3 months.

Once a clinical program is transferred or assigned to a CRO, and the CRO is up-to-speed on the device and the program objectives, the clinical project planning and study design begin in earnest. This is true regardless of whether the study is a pilot study or a pivotal trial. A significant portion of clinical project planning is focused on the development of the clinical protocol. If the sponsor has already written the protocol, a quality CRO is obligated to review the protocol and provide feedback to the sponsor based on their experience. This review will ensure the protocol meets the sponsor’s objectives, is thoroughly understood by the CRO, has no show-stopping scientific issues or regulatory concerns, is workable/practicable, and has the highest probability of success.

If the sponsor delegates the protocol development to the new CRO, then the new CRO will need to address all of the components of the protocol—including, but not limited to: study type, patient eligibility criteria, sample size, patient management procedures, monitoring plan, data analysis plan, investigator numbers, criteria and locations, etc., — with a learning curve starting at the beginning.

Protocol development by a new CRO can typically take up to roughly 3 months to complete and will be on the critical path. When NAMSA performs both the preclinical and clinical programs, these protocol activities come out of the critical path and are performed concurrent to the preclinical program.

Once a fully approved protocol is available, it is usually 3 to 6 months before the first patient can be enrolled. Most often, this is caused by delay in getting the investigative sites identified, contracted, and set up. Because NAMSA clinical personnel are engaged so early in the preclinical studies,
NAMSA can typically shorten this time as well. We can begin to identify potential sites, and start conversations with key investigators during the implementation of the preclinical program, giving a jump-start to the clinical study as FDA is reviewing the study design and preclinical results.

**Summary**

The old saying goes, “If you do what you have always done, you will get what you have always gotten.”

Significant time savings are available in the development of medical devices. However, to achieve these savings, both the sponsor and the contract research partner must behave differently than they typically do today. When a medical device company uses NAMSA, the medical research organization, for both the preclinical and clinical portions of their development, and NAMSA employs the techniques and strategies described herein as much as 6 months may be cut from the product development timeline. Table 1 summarizes how these savings can be attained.
<table>
<thead>
<tr>
<th>Activity Area</th>
<th>Typical Time to Complete</th>
<th>Notes</th>
<th>Typical Time to Complete</th>
<th>Notes</th>
<th>Time Saved</th>
<th>Development Timeline Critical Path?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical Vendor Identification andQualification</td>
<td>5 weeks</td>
<td>Includes vendor selection, paper and site audits, etc.</td>
<td>6 weeks</td>
<td>Combining preclinical and clinical services with one vendor means a little more time is spent up front, but there is time savings realized in clinical vendor selection.</td>
<td>-1 week</td>
<td>Yes</td>
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<td>Preclinical Services Contract</td>
<td>3 weeks</td>
<td>Includes MSA and work statements.</td>
<td>3 weeks</td>
<td>1 MSA with 1 vendor (instead of 2) covering both preclinical and clinical services; savings comes in with the clinical contract.</td>
<td>0 weeks</td>
<td>Yes</td>
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<tr>
<td>Preclinical Study Design/Project Planning</td>
<td>4 weeks</td>
<td>Includes staffing, test model acquisition, IACUC review and approval, draft protocol and CRF development, review and finalization, and study team training and introductions.</td>
<td>4 weeks</td>
<td>NAMSA clinical staff will participate in preclinical protocol design and preclinical CRF development, and will attended preclinical cases.</td>
<td>0 weeks</td>
<td>Yes</td>
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<tr>
<td>IACUC Approval</td>
<td>6 weeks</td>
<td>It typically takes 1 to 2 months for IACUC approval through an independent IACUC.</td>
<td>2 weeks</td>
<td>NAMSA has its own IACUC. Typical approval time through NAMSA IACUC is 1 to 2 weeks.</td>
<td>4 weeks</td>
<td>Yes</td>
</tr>
<tr>
<td>Clinical Vendor Identification andQualification</td>
<td>5 weeks</td>
<td>Includes vendor selection, paper and site audits, etc.</td>
<td>0 weeks</td>
<td>Combining preclinical and clinical services with 1 vendor means the elimination of the clinical vendor qualification exercise.</td>
<td>5 weeks</td>
<td>No</td>
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<tr>
<td>Clinical Services Contract</td>
<td>3 weeks</td>
<td></td>
<td>0 weeks</td>
<td>The MSA was negotiated to cover both preclinical and clinical services.</td>
<td>3 weeks</td>
<td>No</td>
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<td>Transition from Preclinical to Clinical</td>
<td>10 weeks</td>
<td>It typically takes 2 to 3 months to onboard a new clinical CRO, and get the team up to speed. This includes training, review of preclinical studies, review and buy into clinical protocol, etc.</td>
<td>0 weeks</td>
<td>Because NAMSA’s clinical staff has participated in preclinical protocol design, preclinical CRF development, regulatory meetings, and preclinical cases, they will have had extensive experience with and knowledge of the device during the preclinical portion of the development process. Only required training is necessary with minimal/no onboarding.</td>
<td>10 weeks</td>
<td>Yes</td>
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<td>Clinical Study Design/Project Planning</td>
<td>4 weeks</td>
<td></td>
<td>0 weeks</td>
<td>The clinical study design has been developed and refined during the preclinical development phase.</td>
<td>4 weeks</td>
<td>Yes</td>
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CRF, case report form; IACUC, Institutional Animal Care and Use Committee.

**Table 1. Summary of Time Saved by Using One MRO vs Two CROs**

<table>
<thead>
<tr>
<th>Development Timeline Critical Path?</th>
<th>TOTAL TIME SAVINGS</th>
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<tbody>
<tr>
<td>Yes</td>
<td>25 weeks</td>
</tr>
<tr>
<td>No</td>
<td>17 weeks</td>
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REFERENCES


