Lean Six Sigma in Research:

Process Improvement, Minimizing Waste, CAPAs, and More…

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The organization will execute a phased, full deployment of Lean Six Sigma (LSS) to accelerate Business Transformation by creating a culture of continuous, measurable improvement that eliminates non-value-added activities and improves quality and responsiveness for patients and customers.
• Improve the effectiveness (quality) of processes by identifying and removing the causes of defects (errors) and variation

• Improve the efficiency of processes by identifying and removing sources of waste within the process

• Improve the effectiveness and efficiency based on outputs that are critical to Participants
WHAT IS LEAN SIX SIGMA?

- Lean Methods:
  - Remove non-value added waste (TIMWOOD)
  - Therefore, improving speed or process lead time
- Six Sigma Methods:
  - Grounded in the DMAIC methodology
  - Attacks variation
  - As a result, improving quality
- Combined, Lean and Six Sigma
  - Faster cycle times, decreased costs, and improved quality
  - Hence, more satisfied patients
Introducing DMAIC

- The foundational methodology of Lean Six Sigma
- Intentional focus on data

1. **Define**: Describe the problem quantifiably, visualize the process, and understand customer needs
2. **Measure**: Understand the process and its current performance
3. **Analyze**: Identify the true root cause(s) that has the biggest impact on process performance
4. **Improve**: Brainstorm and develop improvement solutions to attack root cause(s)
5. **Control**: Implement the solutions and sustain the gains
Purpose: To have the team and its sponsor reach agreement on the scope, goals, and financial and performance targets for the project.

Define:
- Problem Statement
- Goal Statement
- Key Players
- SIPOC Map (Suppliers, Inputs, Process boundaries, Outputs, Customers [patients])
- Process Map
Define Solidify Project Charter

Project Identification & Selection

Team Launch

Gather VOC/VOB

Solidify Project Charter

Process and “Pain” Clearly Defined and Understood

Process Map

Translate to CCRs

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<th>Process</th>
<th>Outputs</th>
<th>Customer</th>
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**PROJECT CHARTER**

**Business Impact**
- Why should we do this? What is the benefit?
- What is the quantified value of the project (in $$$)?
- How does this project align with the business strategy?

**Opportunity or Problem Statement**
- What “pain” are we or our customers experiencing?
- What is wrong or not working?
- Why do we think we can generate the value proposition described in the Business Case?

**Goal Statement**
- Specifically, what are we going to do and deliver?
- What are our improvement objectives and targets?
- How will success be measured? What specific parameters will be measured? Define Y = f(x)

**Project Scope**
- What are the boundaries of the initiative (start and end steps of the process)?
- What authority do we have?
- What is not within scope?

**Project Plan**
- What are we going to complete the work?
- What are the major milestones?

**Team Selection**
- Who are the team members?
- What is their role?
- How much of their time will be dedicated to the project?
Define:

• Problem statement
  • Patient appointment request process is not meeting speed, quality, nor cost expectations… Call wait time is 25 minutes

• Goal Statement
  • Decrease call wait time from 25 minutes to 5 minutes within 6 months

• Key Players
  • Voice of Customer/Patient
  • Voice of business

• Process Map
What Is a Process Map?

- A graphical representation of a process flow identifying the steps of the process and opportunities for improvement

- Types of process maps:
  - Top Down Chart
  - Flow Chart
  - Spaghetti Diagram
  - Swim Lane
  - Multi Functional Flow Chart
  - Value Stream Map
**Purpose:** To thoroughly understand the current state of the process and collect reliable data on process speed, quality, and costs that you will use to expose the underlying causes of problems

**Measure:**
- Measurement Systems Analysis & Performance and Capability
- Baseline Statistics
- Measures of Central Tendency
- Control Charts
- List barriers and issues
- Propose quick wins and rapid improvements
Measure

### Data Collection Plan

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<td>12</td>
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### Validate Measurement System

### Baseline Process Performance

#### Sigma Quality Level

1. **Determine number of defect opportunities per unit**: $O = 3$
2. **Determine number of units processed**: $N = 100$
3. **Determine total number of defects made**: $D = 19$
4. **Calculate Defects per Opportunity**: $DPO = \frac{D}{N \times O} = 0.063$
5. **Calculate DPMO**: $DPMO = DPO \times 1,000,000 = 63,333$
6. **Look up the Sigma in the Sigma Table (next slide)**: $\text{Sigma Quality Level} = 3$

### Develop Measures

- **Input**
- **Process**
- **Output**

- Based on process and $Y = f(X)$

### Current Process Performance

- Established

### Update Charter & VSM

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**LSL**

**USL**

**Customer Target**

**Defects**
**Purpose:** To pinpoint and verify causes affecting the key input and output variable tied to project goals. “Finding the critical Xs”

**Analyze:**
- 5 Why’s
- Fishbone Diagram
- Root Cause Verification
- Pareto Charts
- Proposed Quick Wins / Rapid Improvements
- TIMWOOD
Analyze

Determine Critical X’s
\[ Y = f(X) \]

Prioritized Critical Xs & Root Causes

Identify and Remove Waste

Root Cause ID
5 Why’s

Value-Add Analysis

Data Analysis & Hypothesis Testing
Determining the “Critical Factors (X’s)”

\[ Y = f(X) \]

- For example, when a patient calls to schedule an appointment, the wait time to have their appointment scheduled (Y) is a function (f) of:
  - Appointments available
  - # of people answering the phones
  - Representative's knowledge and skills
  - # of people calling at the same time
  - Accuracy of patient information in the “system”

- All of these X's can be defined, measured and improved

- The key questions are:
  - What are the critical X’s?
  - Which X’s need to be improved and controlled to yield a satisfactory result (Y)?
Cause & Effect Diagram

- Also called the Fishbone or Ishikawa Diagram
- Represents the relationship between an Effect (Y) and its potential causes (Xs)

Used to explore all the potential causes (inputs or Xs) of variation that may be impacting the process and resulting in a single effect (output or Y)
Drilling Down to Root Causes
“5 Whys”

- Dive deeper into the “cause” by asking “Why” 5 times
- Get past the surface *symptom* and identify the Root Cause

### Ask "Why?" 5 Times

**Lean Six Sigma projects take too long**

1. Why? Teams don’t have time to work on project
2. Why? Other activities have not been cleared from their duties
   - 3. Why? Project Sponsor and other affected managers not aware that they need to make this happen
4. Why? Project Sponsor and other affected managers have not attended Project Sponsor Workshop
5. Why? ...
Non-Value Add Activities - *WASTE*

1. **T**ransportation (moving material/product from one place to another)
2. **I**nventory (material/product waiting to be processed)
3. **M**otion (excess movement and/or poor ergonomics)
4. **W**aiting (delays caused by shortages, approvals, downtime)
5. **O**verproduction (producing more than is needed)
6. **O**ver-processing (adding more value than the patient is willing to pay for)
7. **D**efects/Rework (correcting mistakes)

Eliminate it
Reduce it
Streamline it
Combine steps
Value-Add Analysis

- **Participant Value Add** – Steps essential to deliver the product or service according to patient requirements. Three criteria:
  1. Transforms the item or service toward completion
  2. Patient cares (would be willing to pay for it)
  3. Done right the first time

- **Non-Value Add Required** – Steps that allow overall greater effectiveness or efficiency in the process or are required due to regulations.

- **Non-Value Add** – **Waste**. Steps that do not qualify as Value Add or Non-Value Add
**Purpose:** To learn from pilots of the selected solution(s) and execute full-scale implementation

**Improve:**
- Develop “To-Be” Process Map
- Implement Pilot Plan, Develop Approved Solution(s) and Detailed Implementation Plan
- Develop Implementation Risk Analysis and Mitigation Plan
- Estimate Operational and Financial Benefits
Improve

Generate Solutions
Idea Generation Techniques
- Brainstorming
- Six Thinking Hats
- Problem Reversal
- Idea Box
- Random Word
- Mind-Mapping
- Lateral Thinking
- Twenty Questions
- Candid Comments
- Musical Chairs
- Building on Ideas
- Challenge Assumptions
- Solution Mapping
- Many Others

Prioritize & Select Solutions

Narrow Solutions

Pilot the Solutions

Solutions generated, prioritized, and piloted

Implementation Plan

Define
Measure
Analyze
Improve
Control
**Purpose:** To complete project work and hand off improved process to process owner, with procedures for maintaining the gains

**Control:**
- Corrective and Preventive Actions (CAPA)
- Revise Process Documentation
- SOPs and Training Plans
- Plan for Transition to Process Owner
- Risk Analysis and Mitigation
- Goal Achievement
Control

Sustaining the Gains

Documentation/SOP’s

Process Control Plan

Poka-Yoke

NEW process in control
Control plan in place
Transitioned to “owner”

Transition Ownership

Control Charts
CAPA Defined:
• Corrective Action: Action to eliminate the cause of a detected nonconformity or other undesirable situation.
• Preventive Action: Action to eliminate the cause of a potential nonconformity or other undesirable situation.

Preventive action is taken to prevent occurrence whereas corrective action is taken to prevent reoccurrence.

CAPA planning may involve writing new SOP’s or Work Instructions to address deficiencies and/or editing existing SOP’s/WI.

When creating corrective action plans, the individual(s) involved in the issue will be engaged to assist in identifying corrective action steps they can agree to and implement.
FDA Regulatory Expectations:
• Do you have a well designed plan?
• Have you done what was planned?
• Did you check for the presence of errors?
• Did errors that matter occur and were you able to identify them?
• When errors occurred, how were they handled to ensure subject protection and data integrity?
• Was an appropriate CAPA promptly instituted, communicated, tracked and revised as needed?
• Did you document this process so that it is transparent to regulatory authorities?
The key steps in control and your CAPA are:

- Develop supporting methods and documentation
- Launch implementation
- Lock in performance gains
- Monitor implementations
- Develop process control plans and hand off control to the process owner
- Audit the results
- Finalize the project
- Validate performance and financial results
CAPA DECISION FLOW CHART

Have CAPA system procedures that address the requirements of the QS regulation been defined and documented?
820.100(a) (1)

Existing Problems - Corrective Actions
Were quality data sources identified? Have data from these sources been analyzed to identify existing product and quality problems that require corrective action?
820.100(a)(1) (2)

Potential Problems - Preventive Actions
Were sources of product and quality information that may show unfavorable trends identified by the firm? Have data from these sources been analyzed to identify potential product and quality problems that may require preventive action?
820.100(a)(1) (3)

Are the data received by the CAPA system complete, accurate and timely?
820.100(a)(1) (4)

a. Are appropriate statistical analysis methods used?
b. Are results of analyses compared across different data sources to identify and develop the extent of product and quality problems?
820.100(a)(1), 820.250 (5)

Investigating Cause
a. Are failure investigation procedures followed?
b. Is the failure investigation commensurate with the significance and risk of the nonconformity?
c. Are failure analyses conducted to the root cause, where possible?
d. Is there control to prevent the distribution of nonconforming product?
820.100(a)(2), 820.90(b) (6)

Has appropriate corrective action been taken for significant product and quality problems identified from data sources?
820.100(a)(3) (7)

Were corrective and preventive actions:
  a. effective?
  b. verified or validated prior to implementation?
820.100(a)(4) (8)

Are corrective and preventive actions for product and quality problems implemented and documented?
820.100(a)(5), 820.100(b) (9)

Has information regarding nonconforming product, quality problems and corrective and preventive actions been properly disseminated?
820.100(a)(6), 820.100(a)(7) (10)

Evaluate subsystem for adequacy based on findings.

Continue inspection of other subsystems.

CORRECTIVE AND PREVENTIVE ACTIONS (CAPA) DECISION FLOW CHART
Lean Six Sigma (LSS) accelerates transformation by creating a culture of continuous, measurable improvement that eliminates non-value added activities and improves quality and responsiveness for patients and participants.

The complexity of research, high costs, and delays has an impact on patients and the public.

Need for more effective and efficient research

Lean Six Sigma and Process Improvement projects
  - Standardize performance metrics
  - Drug discovery
  - IRB approval
  - Clinical trial activation
  - Minimize deviations
Improving Clinical Trial Activation Using Lean Six Sigma Methodology

Amelia Schmidt, MHA, CCRP; Theresa Cummings, RN, MS, CCRP; Jennifer Richards, MS, CCRP

Clinical trial activation at an Academic Institution involves a multitude of stakeholders that include but are not limited to the hospital, the University, and the financial departments of both. Lean Six Sigma (LSS) methodology accelerates business transformation by creating a culture of continuous, measurable improvement that eliminates non-value-added activities and improves quality and responsiveness for patients and customers.

The experience at the University of Maryland Greenebaum Comprehensive Cancer Center revealed that delays and barriers throughout the trial activation process lead to considerable time loss in activating our site and opening a study to accrual. This has led to lower patient accrual, termination as a participating site and wasteful use of resources.

In a series of root cause analyses conducted at UMGCCC by a LSS green belt, we determined the following were the most significant and impactful contributors to delayed trial activation: lack of Scientific Review Committee (SRC) meetings; delay in calendar creation in our online Clinical Trial Management System (CTMS); Sponsor unresponsiveness leading to a delay in IRB submission; and delayed completion of the Coverage Analysis and finalization of budgets and contracts.

**Goals**

- To improve efficiency of trial activation
- To reduce median activation time by 40%
- Protocol assigned and reviewed by SRC within 4 weeks of site approval
- Lower calendar creation time in the CTMS to less than 8 days

**Methods**

- Implemented a 3rd SRC meeting per month and added more members and reviewers to the committee. Added a regulatory resource and dedicated CRC coordinator to accommodate this.
- Improved Calendar creation process in the CTMS system by revising the work flow to improve, define, and minimize steps and time involved in the process.
- Education of all CRO staff of the revised study activation timeline.
- Assessed and communicated the obstructions that were found using LSS Methodology. These findings were communicated to Hospital and University management that are overseeing Coverage Analysis and Budget and Contract negotiation.

**Results**

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**Conclusion**

Using Lean Six Sigma Methodology and the DMAIC process, we defined, measured, analyzed, improved, and continue to control underlying causes, waste, and barriers. In doing this, we identified and implemented two process improvement initiatives to improve study activation timelines and were able to improve the speed, quality, and cost of study start up. In addition, we established two new methods of communication and training of staff to increase transparency and “buy-in” to Six Sigma methodology across the team.

Implementation of a third SRC meeting eliminated the immediate backlog of new clinical trial reviews and allowed more time for the possibilities of re-reviews and emergency use protocols while still providing time slots for full reviews.

Through 10 Root Cause Analyses, UMGCCC built process maps, conducted baseline statistics, performed measures of central tendencies, and created pareto charts. In doing this, a significant difference was seen in the trial activation timeline.

**Future Directions**

This work demonstrates that LSS Methodology can be applied to operational issues in clinical research, including clinical trial activation. Ensuring the research team within a designated cancer center includes a staff with LSS experience/certification ensures the resources and knowledge exist to apply the methodology effectively. Sharing results with key stakeholders outside of the research office is critical to allow visibility to the outcome of the problems identified. Future directions for GCCC include performing a quarterly review of randomly selected trials. This allows UMGCCC leadership to perform risk analysis and mitigation, establishmodify goals and review results for further revision of process documentation as needed.
1688GCC “Current State” Regulatory Process Map

PI & Reg Coordinator
- PI completed SVQ [05/25/2016] (71 days)
- Sponsor sent necessary docs [8/4/2016] (39 days)
- GCC number and CRC meeting date [8/4/2016] (39 days)
- Reg Co. inputs study into OnCore [9/12/2016]
- Contracts Dir. Informed of OnCore completion [9/12/2016]

CRC
- RC sent reminder email to Sponsor [11/16/2016] (3 days)
- Sponsor responded to RC email with CICERO answers [9/15/2016] (5 days)
- SC asked RC for Study Protocol [9/20/2016] (5 days)
- RC provided SC Study Protocol [9/20/2017] (27 days)

- RC sent COI, Pharmacy, & Welcome email [9/12/2017] (3 days)
- Sponsor sent final ICF [11/22/2016] (23 days)
- Sponsor no longer pursuing UMGCCC as a site. IRB submission not done [1/11/2017]

MCA
- MCA Assigned to reviewer [12/18/2016] (18 days)
- MCA Submitted to UMBiz [11/30/2016] (2 days)
- Con. Dir. Creates R vs. SOC [11/28/2016] (5 days)
- Calendar imported [11/23/2016] (23 days)

Note: 1688GCC: The Protocol Approval Time (only to submit to IRB) was 166 days. This does not meet customer expectations.
Critical Xs That are Causing the Y (Effect)

(Y) Effect: Trial Activation is > 3 months
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Future Directions

This work demonstrates that LSS Methodology can be applied to operational issues in clinical research, including clinical trial activation. Ensuring the research team within a designated cancer center includes a staff with LSS experience/certification ensures the resources and knowledge exist to apply the methodology effectively. Sharing results with key stakeholders outside of the research office is critical to allow visibility to the outcome of the problems identified. Future directions for GCCC include performing a quarterly review of randomly selected trials. This allows UMGCCC leadership to perform risk analysis and mitigation, establish/modify goals and review results for further revision of process documentation as needed.
Note: Following SOPs and Work Instruction Guidelines, the Study Start up Process will take 28 days.
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Minimizing Clinical Trial Deviations Through Lean Six Sigma and a CRO Compliance Committee

Amelia Schmidt, MHA, CCRP; Jill Kessler, MS, CCRP; Theresa Cummings, RN, MS, CCRP

Purpose

The University of Maryland Greenebaum Comprehensive Cancer Center Clinical Research Office (UMGCCC CRO) Compliance Committee reported an abundance of re-occurrences and similar occurrences of clinical trial deviations deriving from research specimen collections and sample management.

The purpose of this project was to analyze and determine the root causes of lab and sample deviations, to improve sample collection, and minimize research lab errors and deviations.

In a root cause analyses conducted at UMGCCC by a Lean Six Sigma Green Belt, we determined the following were the most significant causes of sample collection RNIs and deviations.

- Inconsistent performance of procedures
- Lack of quality control processes
- Inconsistent usage of the calendar of events
- Staffing of the lab and medical assistant teams.

Methods

- **Define:** Using Lean Six Sigma (LSS), we identified and defined the problem statement that the amount of deviations in 9 months (n=55) was too high and set a goal to minimize the errors by 50% in 6 months.
- **Measure:** Created a “current state” process map of the lab and sample collection process. Through creating the process map, we were able to look at the path of sample collection and define cost value added, no value added but required, and no value added processes.
- **Analyze:** By creating a fishbone diagram, we were able to identify the effect (Y): research lab deviations and then identify the Critical (X): root causes. We were then able to prioritize the root causes and propose quick wins and rapid improvements.
- **Improve:** Through prioritizing the root causes, we then were able to prioritize a list of solutions. We created a “future state” process map of sample collection and came up with a pilot plan.
- **Control:** In the control phase, we revised process documentation, updated SOPs and training plans, and planned to transition sample management to the process owner. These improvements were implemented in April 2019 and is currently an active project. The re-evaluation date is set for October 2019.

Goals

- The immediate goal of this project was to determine the root causes of sample collection RNIs and deviations.
- To improve lab collection and minimize research lab errors and deviations.
- The long term goal of this analysis is to reduce the sample management error rate by at least 50% in the next 6 months by implementing solutions for deviations.

Results

- Updated the Research Specimen & Procedure Management SOP
- Implemented quality control training
- Updated the processes for calendar entry of research specimen collection requirements
- Provided supporting evidence and documentation that a Clinical Lab Coordinator management position was necessary for the CRO. This position was filled and the coordinator took over as the “process owner”

Conclusions

This work demonstrates that LSS methodology can be applied to operational issues in clinical research, including clinical trial deviations. By identifying root causes and prioritizing solutions, the UMGCCC CRO Compliance Committee was able to review and discuss the deviation report descriptions, brainstorm causes for deviations, discuss possible solutions for deviations, and mitigate strategies to be relayed by the CRO leader representative. Future directions for GCCC include creating a monthly compliance report and quarterly reviews of research specimen and management deviations. This will allow UMGCCC leadership to perform risk analysis and mitigation, establish/modify goals and review results for further revision of process documentation as needed.
Critical Xs That are Causing the Y (Effect)

Calendar
- No template calendar entry
- SC unaware of lack of MA staff
- No access to calendar for instructions
- Allo Clinic staff had to conduct draw

Quality Assurance
- Multiple draws at same time point
- Calendar uniformity
- Inconsistencies in procedures
- Kit inventory/reordering updates
- Training of QC and attention to detail
- No QC once samples were shipped
- No QC of kits pulled were drawn
- No QC once samples were drawn
- Calendar not QC'd

Staff
- No MA available for blood draw
- Allo not trained on Protocol
- 2 of the 3 MAs were in office

Quality Control
- No QC once samples were shipped
- No QC of kits pulled were drawn
- Calendar not QC'd

(Y) Effect: Research Lab RNI/Deviation
Kit is dropped off to Clinic [day of visit]

Patient arrives in Clinic [day of visit]

Clinic calls MAs for lab draw [day of visit]

MAs pull study specific kit for study visit [day of visit]

MA reviews Calendar [afternoon prior to visit]

MAs complete draw [day of visit]

MAs package and freeze samples [per protocol instructions]

MA ships samples [per protocol instructions]

Requisition form(s) QC’d [before shipment]

Data Manager enters data into CTMS system

Documentation produced during collection, processing and shipment is given to SC for inclusion in the patient research shadow chart

If any changes are made to the calendar after 3pm the evening before a visit, the SC must verbally communicate changes to the MAs [day of visit]

Enters appointment information to shared calendar [before COB day prior to draw]

MA ships samples [per protocol instructions]

Requisition form(s) QC’d [before shipment]

Data Manager enters data into CTMS system

Green (CVA); Amber (NVA-R); Red (NVA)
Minimizing Clinical Trial Deviations Through Lean Six Sigma and a CRO Compliance Committee

Amelia Schmidt, MHA, CCRP; Jill Kessler, MS, CCRP; Theresa Cummings, RN, MS, CCRP

Purpose

The University of Maryland Greenebaum Comprehensive Cancer Center Clinical Research Office (UMGCC CRO) Compliance Committee reported an abundance of re-occurrences and similar occurrences of clinical trial deviations deriving from research specimen collections and sample management.

The purpose of this project was to analyze and determine the root causes of lab and sample deviations, to improve sample collection, and minimize research lab errors and deviations.

In a root cause analyses conducted at UMGCCC by a Lean Six Sigma Green Belt, we determined the following were the most significant inconstant performance of procedures, lack of quality control processes, inconsistent usage of the calendar of events, and staffing of the lab and medical assistant teams.

Goals

- The immediate goal of this project was to determine the root causes of sample collection RNIs and deviations.
- To improve lab collection and minimize research lab errors and deviations.
- The long term goal of this analysis is to reduce the sample management error rate by at least 50% in the next 6 months by implementing solutions for deviations.

Methods

- Define: Using Lean Six Sigma (LSS), we identified and defined the problem statement that the amount of deviations in 9 months (n=55) was too high and set a goal to minimize the errors by 50% in 6 months.
- Measure: Created a “current state” process map of the lab and sample collection process. Through creating the process map, we were able to look at the path of sample collection and define cost value added, no value added but required, and no value added processes.
- Analyze: By creating a fishbone diagram, we were able to identify the effect (Y): research lab deviations and then identify the Critical (X): root causes. We were then able to prioritize the root causes and propose quick wins and rapid improvements.
- Improve: Through prioritizing the root causes, we then were able to prioritize a list of solutions. We created a “future state” process map of sample collection and came up with a pilot plan.
- Control: In the control phase, we revised process documentation, updated SOPs and work instructions, performed risk analysis and mitigation, establish/modify goals and strategies to be relayed by the CRMO leader representative.

Results

- Updated the Research Specimen & Procedure Management SOP
- Implemented quality control training
- Updated the processes for calendar entry of research specimen collection requirements
- Provided supporting evidence and documentation that a Clinical Lab Coordinator management position was necessary for the CRO. This position was filled and the coordinator took over as the “process owner”

Conclusions

This work demonstrates that LSS methodology can be applied to operational issues in clinical research, including clinical trial deviations. By identifying root causes and prioritizing solutions, the UMGCC CRO Compliance Committee was able to review and discuss the deviation report descriptions, brainstorm causes for deviations, discuss possible solutions for deviations, and mitigate strategies to be relayed by the CRO leader representative.

Future directions for GCCC include creating a monthly compliance report and quarterly reviews of research specimen and management deviations. This will allow UMGCC leadership to perform risk analysis and mitigation, establish/modify goals and review results for further revision of process documentation as needed.
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• https://wwwapp1.bumc.bu.edu/ocr/ClinicalResearchNewsletter/article.aspx?article=349

QUESTIONS?

THANK YOU!