LIVE WEBINAR

Revolutionizing Medical Device Trials with Risk-Based Monitoring (RBM)

April 16, 2024 | 9 am ET / 3pm CET

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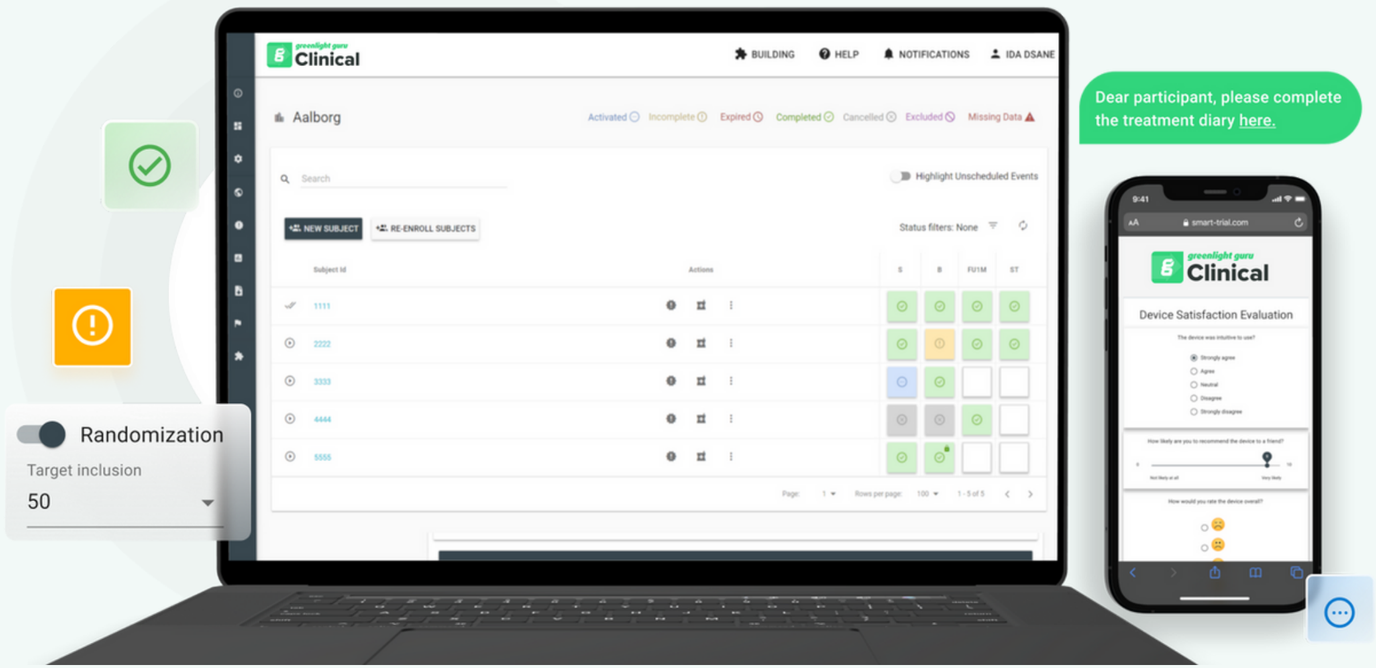

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Today's Speakers

Helene Quie
CEO,
Qmed Consulting

Chris Rush
Solutions Engineer,
Greenlight Guru

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Risk Based Monitoring

Helene Quie, CEO
Qmed Consulting A/S

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Agenda

- Introduction to Risk Based Monitoring (RBM) principles.
- Regulatory landscape and guidance specific to medical device clinical studies.
- Identification and assessment of risks in medical device trials.
- Implementing risk-based monitoring strategies tailored to medical devices.
- Challenges and best practices in adopting RBM for medical devices.
- Future directions and emerging trends in RBM for medical device clinical studies.
- Real-world case studies demonstrating successful RBM in medical device trials.

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Principles of Risk Based Monitoring (RBM)

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What is RBM?

- **An adaptive approach to clinical trial monitoring that directs monitoring focus and activities to the evolving areas of greatest need which have the most potential to impact patient safety and data quality.**

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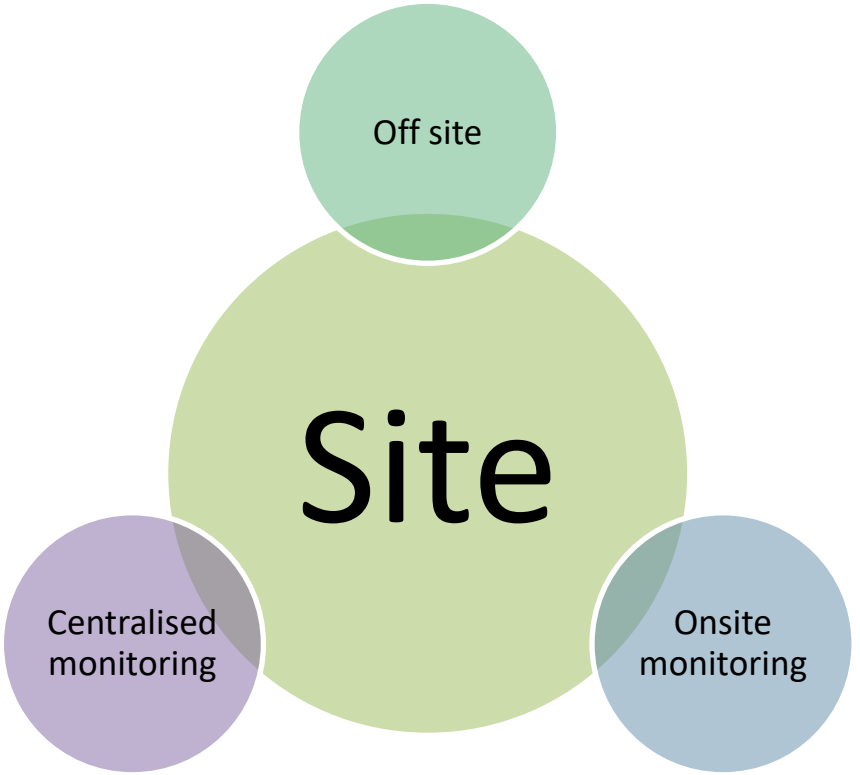
Type of Monitoring



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Type of Monitoring

On-site monitoring

- In person evaluation
- CRF review and SDV
- Sense of quality of study conduct
- Access compliance with protocol and IP accountability
- Evaluate Investigator oversight
- Engaging and coordinates in person with site staff
- Verifying facility and equipment, and overall quality conduct
- Assure study documentation exists
- Look for data inconsistencies
- Assess site staff compliance and training
- Device accountability

Off-site monitoring

- Data review
- Supporting questions from sites
- Confirm timeliness and quality of data entry
- Review of query resolution
- Review of CRF to check protocol compliance
- Confirm site's completion of previously identified actions
- Access site's recruitment and enrolment
- Conduct training'

Centralised monitoring

- Monitoring data quality and critical data reporting
- Enacting proactive and early identification of quality, safety and operational risks based on the continuous monitoring of data and the risk indicators
- Tracking site performance metrics
- Triggering proposed site contacts and on-site visits based on issues that are identified
- Review data in real-time
- Conduct analysis of data & site performance
- Remote evaluation of data
- Checks of range and completeness of data
- Review data distribution
- Identify high risk sites
- Statistical analysis to identify data trends
- Conduct SDV if possible

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What is the regulatory frames?

International guidance ISO 14155	FDA Guidance	EMA Reflections Paper	TransCelerate Paper	Clinical Trials Transformation Initiative (CTTI)
ISO14155 -Introduction of risk-based monitoring and risks associated with the investigational device linked to ISO 14971	Quality Clinical Trial Data -Assess Risk -Combination of monitoring activities Tailor Monitoring Plan https://www.fda.gov/media/121479/download	Risk Based Quality Management -Plan -Adapt -Build on experience and advances Reflection paper risk based quality management in clinical trials (europa.eu)	RBM Methodology -Holistic, proactive approach; risk assessment, mixture of remote & on-site monitoring Risk Based Monitoring Solutions - TransCelerate (transceleratebiopharmainc.com)	Quality by Design -Tailor monitoring approach -Protocol quality impacts monitoring quality Clinical Trials Transformation Initiative - CTTI (ctti-clinicaltrials.org)

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How does RBM differ from On-site Monitoring?

- Customize approach
- Identifies potential issues proactively
- Leverages technology
- Relies on central monitoring
- Used a a trigger for on-site monitoring

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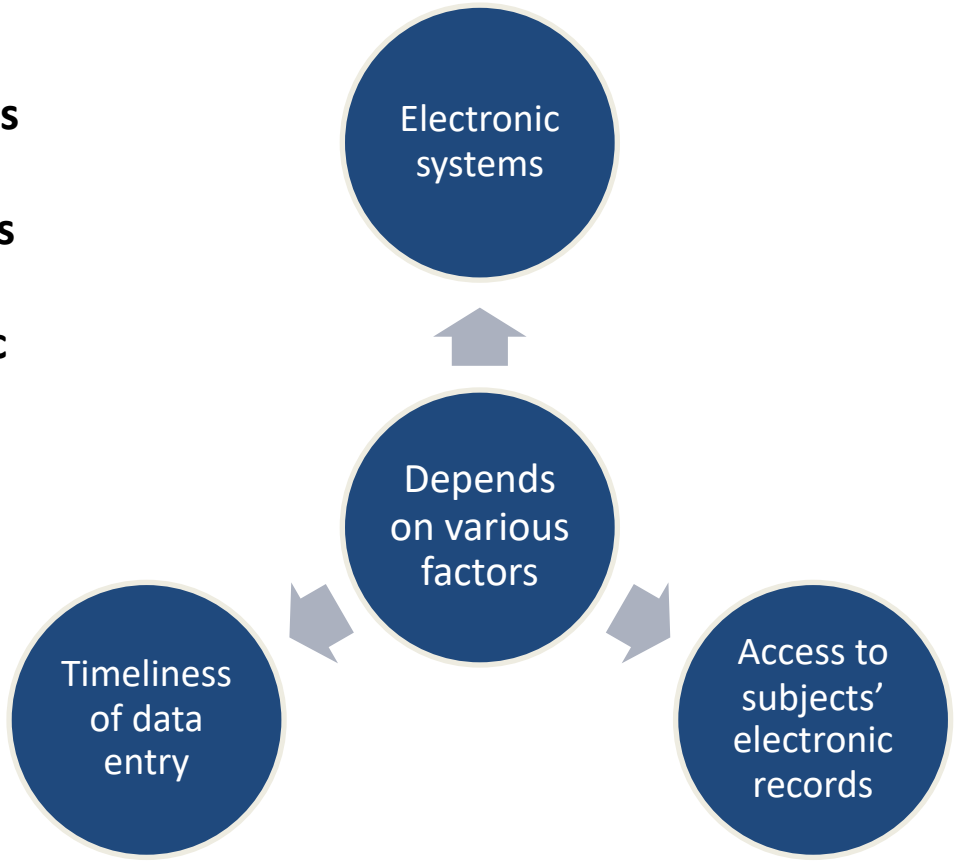
Centralised Monitoring

- **Takes an integrated approach to assess risk and more appropriately allocates resources to the sites.**
- **An algorithm assess the riskiness of each site by taking into consideration fixed and dynamic risks.**
- **The outcomes of centralised monitoring and statistical data review can trigger automated and nonautomated intervention in the study.**



Remote Monitoring

- Uses lower-cost resources to conduct investigator telephone calls, remotely monitor data, and perform other monitoring activities that do not require on-site resources.
- Remote monitoring supplements reduced on-site SDV to help ensure maintenance of patient safety and data integrity.

Often practiced at large CROs

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Guidelines

ISO 14155:2020 & ICH GCP E6 (R2) •Provide flexibility in how trials are monitored •Advise sponsors to consider the objective, design, complexity, size, and endpoints of a trial in determining the extent and nature of monitoring for a given trial •Quality Management (Risk based Approach) Monitoring Plan	ISO 14155:2020 6.2 Risk Management Risks associated with investigational device and its related clinical procedure shall be estimated in accordance with ISO 14971 prior to design & conduct of clinical investigation	ISO 14155:2020 6.7 Monitoring Plan ⇨ The sponsor shall determine the extent and nature of monitoring appropriate for the clinical investigation based on the risk assessment.' ⇨ The extent and nature of the monitoring, including the strategy for source data verification versus centralized data review (evaluation without visiting the investigation site), subject protection and timely reporting, shall be based on the objective, design, complexity, size, critical data points and endpoints of the clinical investigation and the degree of deviation from normal clinical practice – risk- based monitoring.	ICH GCP Section 5.18.3 'The sponsor should develop a systematic, prioritised, risk-based approach to monitoring clinical trials…… The sponsor may choose on-site monitoring, a combination of on-site and centralised monitoring, or, where justified, centralised monitoring. The sponsor should document the rationale for the chosen monitoring strategy (e.g., in the monitoring plan).' 'Centralised monitoring is a remote evaluation of accumulating data, performed in a timely manner, supported by appropriately qualified and trained persons (e.g., data managers, biostatisticians).'

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Advantages of RBM?

FOCUS MORE ON HIGH VALUE ACTIVITIES

EARLY DETECTION OF ISSUES WITH REAL-TIME REVIEW OF DATA

FOCUS ON STUDY SPECIFIC CRITICAL DATA AND PROCESSES

ENSURE GCP COMPLIANCE

COST REDUCTIONS

TEAM APPROACH – MONITORS, MEDICAL MONITORS, DATA MANAGEMENT & SITE STAFF

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Identification and assessment of risks

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RBM: Process Simplified

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Critical Data:

Data that are critical to the study findings, data that support primary and secondary endpoints and/or data related to subject safety

Critical Processes

Processes that are critical for the reliability of the study findings, related to ensuring subject safety and which satisfy compliance with GCP and regulations

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Examples

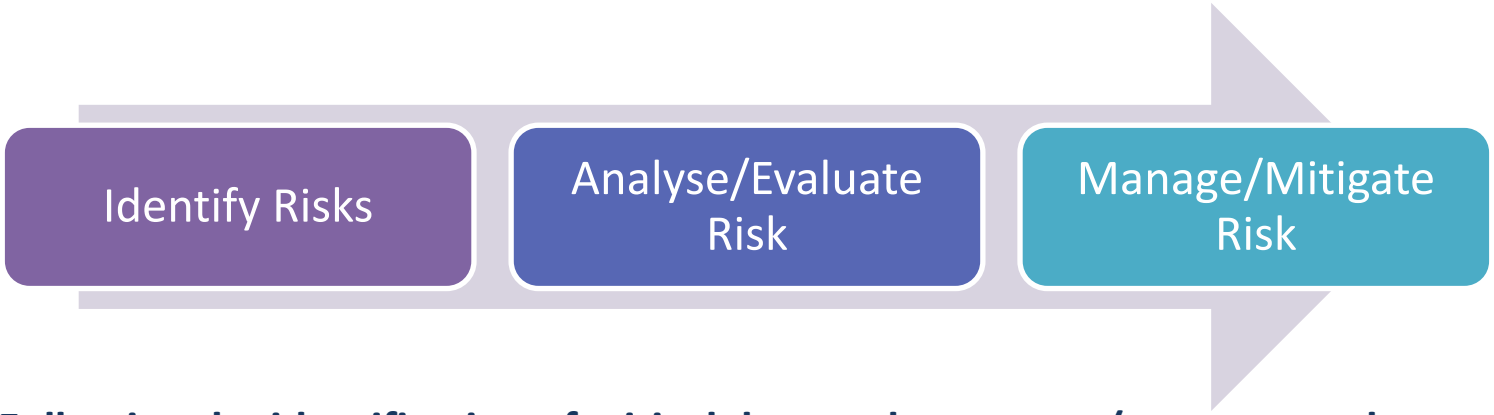
Critical data and processes

- Verification of informed consent process
- Protocol eligibility criteria
- IP accountability
- Study end-points
- Protocol-required safety assessments
- AEs/SAEs

Non-critical Data

- Concomitant treatment
- Demographic characteristics
- Routine laboratory tests performed as part of subject monitoring that do not address protocol specified safety or efficacy endpoints, and
- Processes (e.g. hospital pharmacy's storage of an investigational product with no specific critical handling instructions) identified by the sponsor as non-critical often may be monitored less intensively.

Risk Assessment - Identify Risks



- **Following the identification of critical data and processes (program and protocol level**

- **Perform a risk assessment to identify and understand the nature, sources, and potential causes of risks that could affect the collection of critical data or the performance of critical processes.**

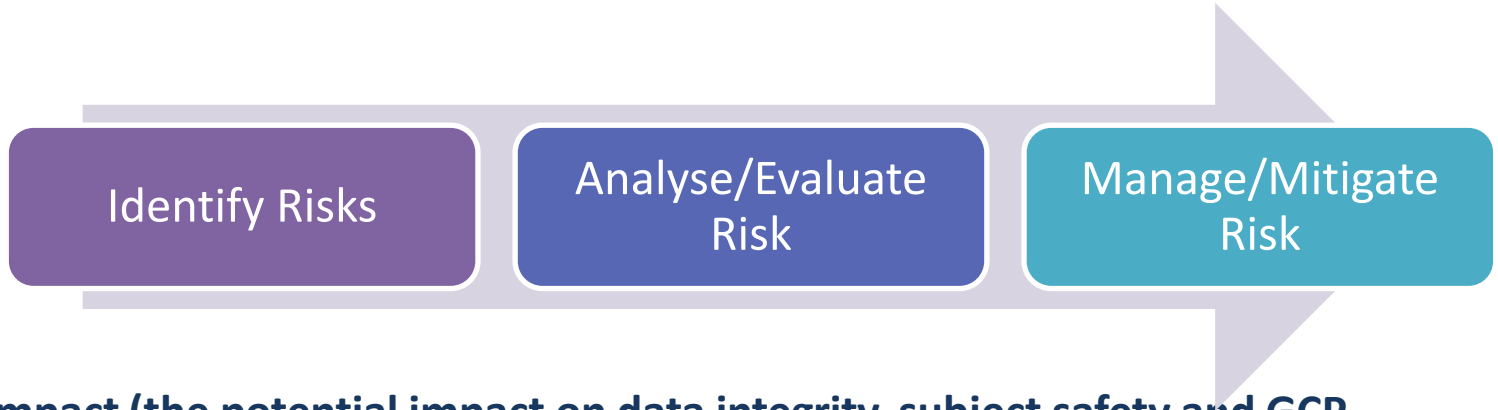
- **Risks to critical data and processes**
  - **↣most merit consideration during risk assessment**
  - **↣ensure monitoring efforts focus on preventing or mitigating important and likely sources of error in their conduct, collection and reporting.**

Risk Assessment - Identify Risks

Risks should be assessed and prioritised by considering the following:

- Likelihood of errors occurring (Probability)
- Impact of such errors on human subject protection and trial integrity (Impact)
- Extent to which such errors would be detectable (Detectability)

Risk Assessment - Analyse/Evaluating Risks



Impact (the potential impact on data integrity, subject safety and GCP compliance for this trial)

Probability (Probability of occurrence)

Detectability (Higher detectability usually means lower risk)

A score can be associated each factor: high (3), medium (2), low (1).

The combined assessment of all of the components determines the risk level.

Risk Assessment – Mitigate Risks

Identify Risks → Analyse/Evaluate Risk → Manage/Mitigate Risk

Once ranked the risks, provide the mitigation actions!

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Implementing risk-based monitoring strategies

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Content of Monitoring Plan

ISO 14155:2020: 6.7 Monitoring Plan

a) The risks associated with the clinical investigation (see 6.2.3) and adequate information on relevant risk control measures;

b) The processes that need to be monitored including data that is required to be verified in source documents;

c) The monitoring methods (on-site, a combination of on-site and where justified, centralized monitoring, as appropriate);

d) The responsibilities;

e) The procedures and requirements for the investigation's oversight;

f) The methods for documenting and communicating monitoring results;

g) The methods for obtaining compliance;

h) The process for escalation in case of continuous or egregious non-compliance;

i) Those aspects of the clinical investigation which need special attention because if performed incorrectly or inadequately, would compromise the protection of human subjects or the integrity of the data;

j) The special requirements regarding personal data protection.

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Challenges and best practices

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Challenges

1. Resource intensive process (costly in time, personnel allocation, and money).
2. Process is subject to time constraints, personnel availability, and data access problems.
3. Lacks scalability to account for the different risk levels of the products being evaluated.
4. With so many resources being deployed for monitoring, both sponsors and regulatory bodies have elevated process execution as a focal point, thereby risking oversight of resultant data implications.

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Major Pitfalls in Risk-Based Monitoring

Besides the essential RBM process implementation components, it is important to be aware of the major pitfalls:

Pitfall #1. SDV is reduced without any other action. A major risk, when under an RBM flag no other actions except the SDV reduction is taken.

Pitfall #2. Risk evaluation is not objective. This may happen if a human factor is involved in risk evaluation.

Pitfall #3. Risk evaluation is biased. Bias is when an interested party is involved in the evaluation. In the economic science, this is called an “agency problem”.

Pitfall #4. Risk evaluation becomes outdated. The risk landscape changes during a trial.

Pitfall #5. Late data arrival. When critical data, essential to the risk analysis, arrives too late for any corrective action. Danger – patient safety.

Pitfall #6. Sites ignore RBM and do not improve. Engaging and involving sites in the RBM initiative is critical to its success.

Pitfall #7. Monitoring team does not accept the new procedure. Why does resistance happen? Change management is required to get the buy-in of all involved. Risk – RBM implementation discontinues.

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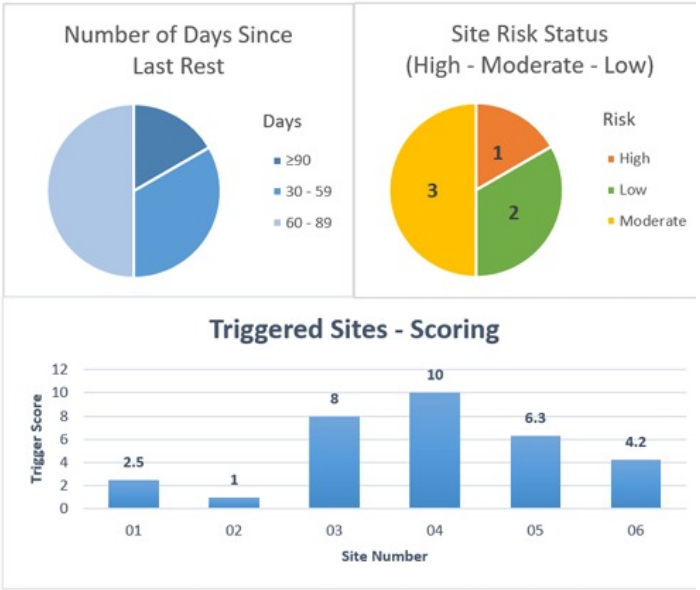
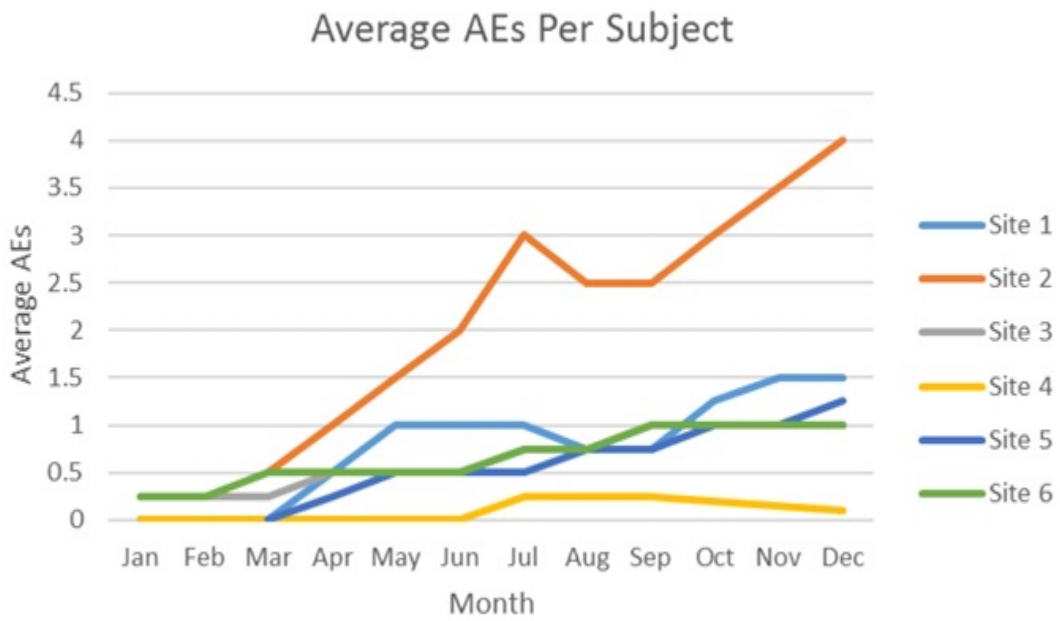
Site #	Trigger Scores
01	2.5
02	1
03	8
04	10
05	6.3
06	4.2





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What does the Future Bring?

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What does the Future Bring?

RBM is a critical approach being evolved to focus on the level of risk posed by the products and studies themselves.

Regulators and industry agrees that efficiency is needed in the monitoring process to manage resources and effort, while maintaining assurance that the data will be reliable, and patients will be protected.

Initiatives from authorities and groups to identify the tools that can be used to accomplish these goals.

Initiatives include the clinical study designs themselves, the means used to capture and maintain data, the potential to leverage technology to examine data, and increased site engagement in the monitoring process.

Successfully advance the monitoring process, realize monitoring effort and risk mitigation economies of scale, ensure patient protections, and provide timely medical device access to patients and providers.

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Insights from Greenlight Guru on Risk-Based Monitoring (RBM)

Chris Rush
Solutions Engineer,
Greenlight Guru

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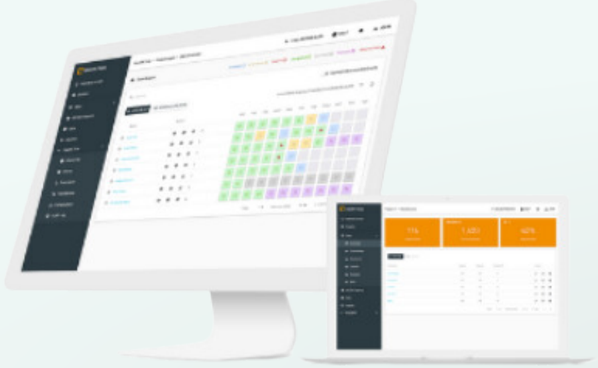
Challenges

- Dispersed study collaborators (on-site & remote)
- Oversight of timeliness and quality of data entry
- Oversight of query resolution
- Assessing site recruitment and enrollment
- Maintaining focus: Critical Data and Non-Critical Data
  - Critical Data: critical to the study findings, data that support primary and secondary endpoints and/or data related to subject safety
  - Non-Critical Data: non-drivers of safety/efficacy endpoints

EDC Software Technology ‘must-haves’

- Facilitate efficient data collection pursuant to Good Clinical Practice (GCP) standards, patient privacy laws
  - ISO 14155:2020, ISO 20916:2019, ICH GCP
  - EU GDPR, HIPAA
- Provide a central data repository for all study activity, for all study collaborators
- Ensure that data changes are documented, data verification and queries are captured in an audit log
- Maintain a secure system to prevent unauthorized use of data, both internally and externally



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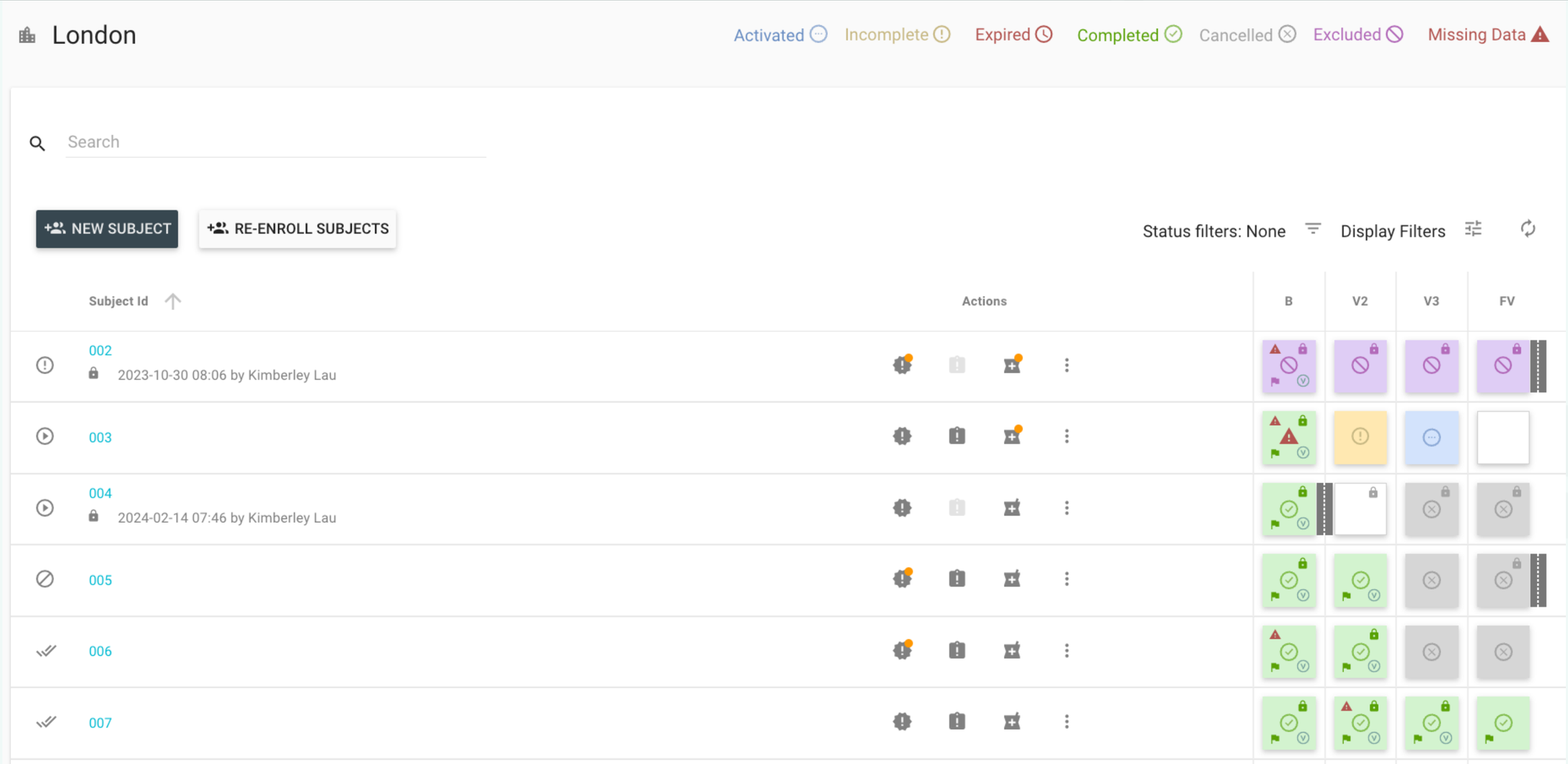
Oversight of timeliness and quality



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Oversight of timeliness and quality

Quick filter

FILTERS 2 | CLEAR ALL FILTERS | COLUMNS | EXPORT AS CSV

Subject Id	Site	Data Event	Status	Verify 1	Verify 2	Lock	Sign off	Activation Date	Complete Date
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002	London	Adverse Event	Reported			No	Yes	2021-01-07 05:20	
003	London	Baseline	Completed	V 22%	V 74%	Yes	No	2021-01-12 07:42	2021-01-13 08:59
003	London	Visit 2	Incomplete			No	No	2024-04-15 16:40	
003	London	Visit 3	Activated			No	No	2021-04-13 08:21	

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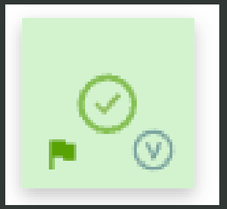
Oversight of query resolution



London

Activated | Incomplete | Expired | Completed | Cancelled | Excluded | Missing Data

Search

NEW SUBJECT | RE-ENROLL SUBJECTS

Status filters: None | Display Filters

Subject Id	Actions	B	V2	V3	FV
002 — 2023-10-30 08:06 by Kimberley Lau					
003					
004 — 2024-02-14 07:46 by Kimberley Lau					
005					
006					
007					

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Oversight of query resolution

Filters

Created by | Status: Open | Subject | CLEAR FILTERS

Site | Data Event | Form | APPLY FILTERS

Search Query Text

Query ID	Status	Subject Identifier	Site	Data Event	Form	Query text	Created by	Created at	Last updated time	Actions
018	Open	005	London	Baseline	Observation	Q	rgb@smart-trial.com	2022-08-16 04:30	2022-08-16 04:30	
021	Open	006	London	Visit 2	Observation second time	please verify	chris.rush@greenlight.guru	2022-09-15 14:30	2022-09-15 14:30	
023	Open	005	London	Baseline	Inclusion/Exclusion Criteria	source data suggests otherwise	chris.rush@greenlight.guru	2022-10-06 03:13	2022-10-06 03:13	
024	Open	005	London	Visit 2	Observation second time	test query	chris.rush@greenlight.guru	2022-11-10 13:44	2022-11-10 13:44	
027	Open	005	London	Baseline	Inclusion/Exclusion Criteria	please confirm	chris.rush@greenlight.guru	2023-02-21 12:46	2023-02-21 12:46	
028	Open	007	London	Baseline	Demographics	please source data verify	chris.rush@greenlight.guru	2023-03-16 16:02	2023-03-16 16:02	
032	Open	005	London	Baseline	Inclusion/Exclusion Criteria	Please confirm this against source data	chris.rush@greenlight.guru	2023-06-12 15:47	2023-06-12 15:47	
037	Open	007	London	Baseline	Demographics	Test query	kimberley.lau@greenlight.guru	2023-06-23 08:43	2023-06-23 08:43	

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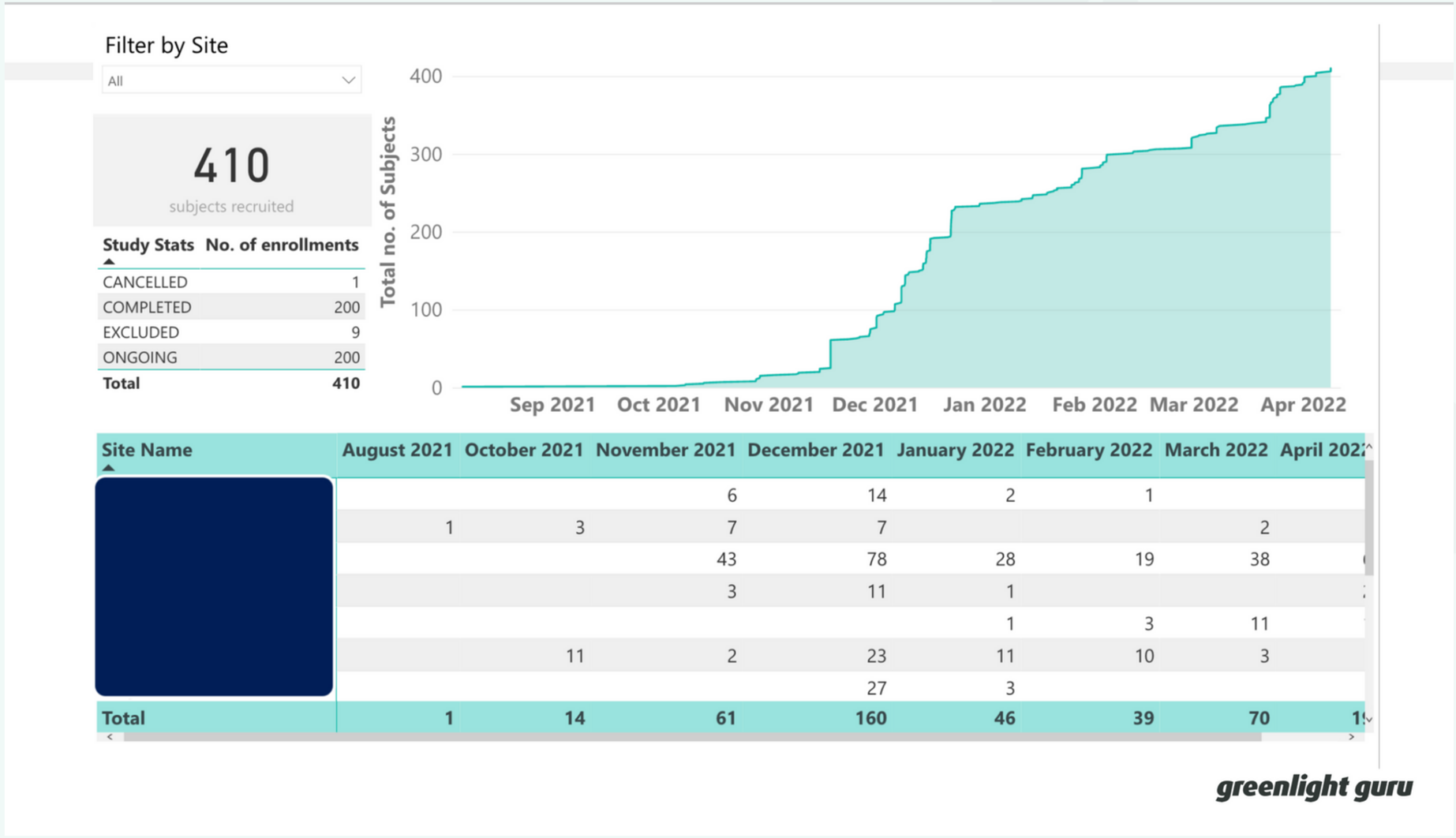
Assessing site recruitment and enrollment



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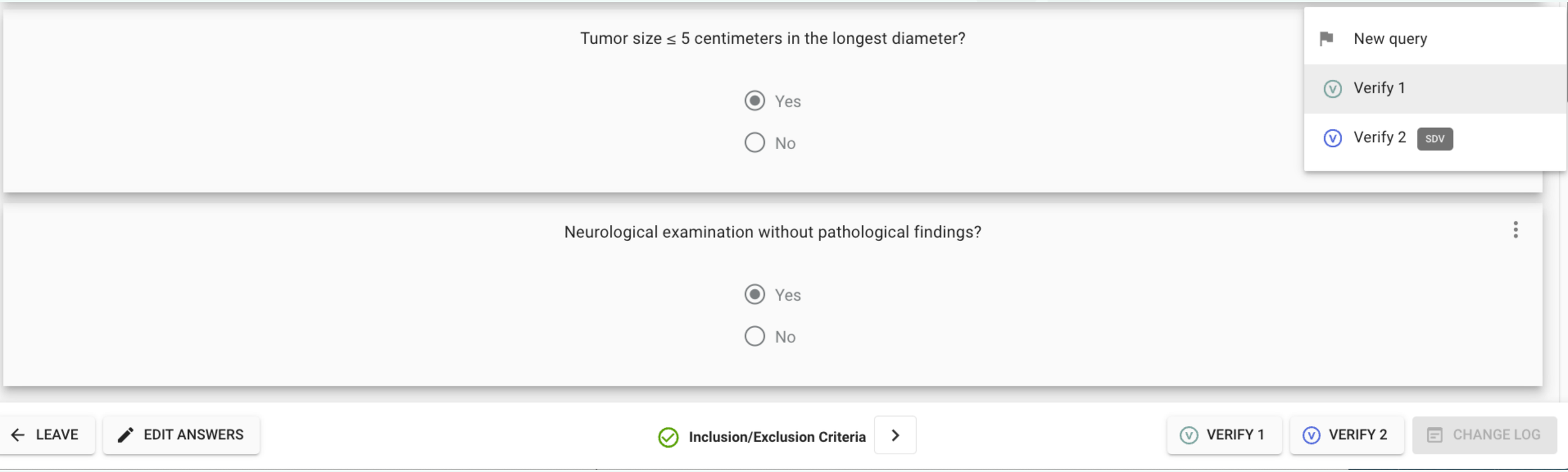
Maintaining focus: Critical and non-Critical



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Maintaining focus: Critical and non-Critical

Quick filter

FILTERS 1 | CLEAR ALL FILTERS | COLUMNS | EXPORT AS CSV

Subject Id	Site	Enrollment St...	Form Updated	Question	Answer	Answer Status	Verify 1	Verify 2	Actions
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003	London	Ongoing	2021-04-28 04:38	Tumor size ≤ 5 centimeters in the longest diameter?	Yes	Completed	No	Yes	>
004	London	Ongoing	2021-06-02 07:53	Tumor size ≤ 5 centimeters in the longest diameter?	Yes	Completed	Yes	Yes	>
005	London	Discontinued	2021-05-04 03:47	Tumor size ≤ 5 centimeters in the longest diameter?	Yes	Completed	Yes	Yes	>
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008	Indianapolis	Ongoing	2022-05-06 14:05	Tumor size ≤ 5 centimeters in the longest diameter?	Yes	Completed	No	No	>

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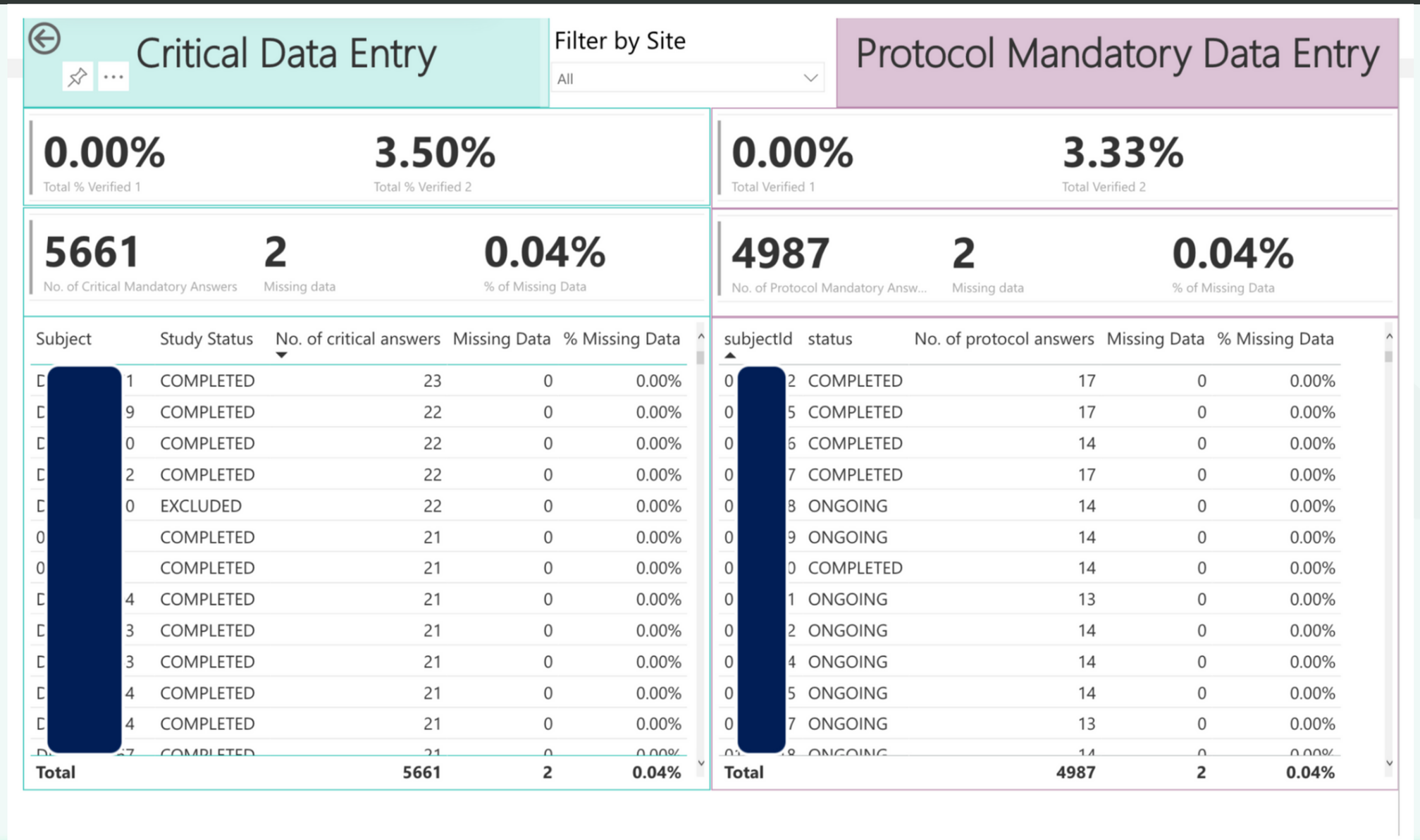
Maintaining focus: Critical and non-Critical



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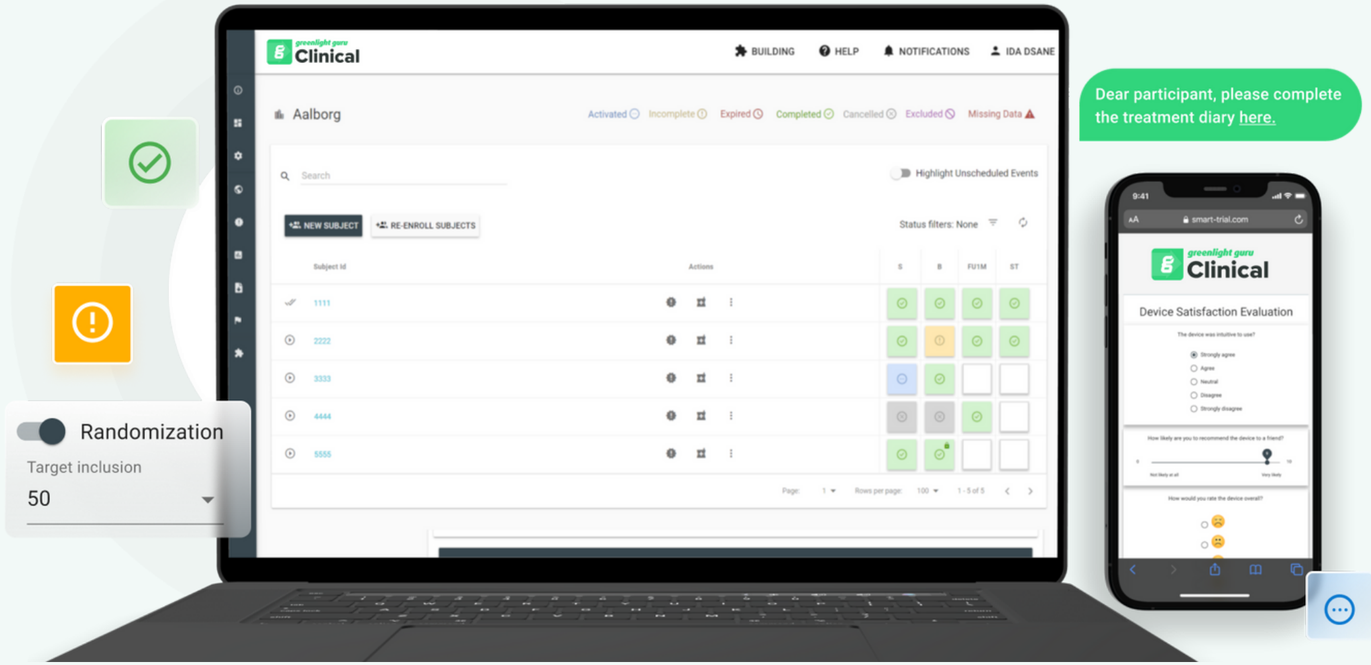
*Formerly **SMART-TRIAL***



The Leading Toolbox for MedTech Clinical Data Collection

A single, compliant platform for collection and management of all clinical evidence, safety, and performance data.

Learn more here: www.greenlight.guru/clinical

Time for

Q&A

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