Paper IC005

The Need for AI Facilitated Monitoring Methods and Techniques to Enhance Participant Safety and Welfare

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ABSTRACT

Within clinical investigations many measures are used to protect participant safety and welfare. Automated tools that signal potential Adverse Events (AEs) pre-emptive for individual is an emerging topic for industry oversight. In this presentation we will demonstrate methodology that can be used to forecast potential AEs during a clinical trial using observed and recorded traits of enrolled individuals. We will then demonstrate how this methodology can be applied within an Artificial Intelligence (AI) framework. The implementation of AI to forecast potential AEs at the level of the individual will allow for rapid risk assessment reports. These reports will offer enhanced participant protection in a way that is pre-emptive rather than reactive. The audience of this presentation will leave with a better understanding of how critical data can be applied within new AI driven tools to protect participant safety and welfare.

INTRODUCTION

Modern clinical trials are designed with participant safety at the core. Trials have strict exclusion criteria for those with known risks for serious interactions with other drugs and medical conditions. Similarly, when signs and symptoms of an adverse event are seen in a participant, study staff are quick to find care for the participant and ensure their well-being. Recent advancements in the emerging field of personalized medicine demonstrate that intervention on adverse events could be more predictive than reactive to better anticipate the risk of having an AE. This shift in thought about how medications effect individuals specifically based on her/his genetic makeup can be applied directly for risk monitoring. Specifically, the medical history, concomitant medications, demographic data, baseline vital signs and other within participant traits can be used to define the participant's phenotype. Expertise also continues to expand with linking phenotypes with genotypes.

The literature is growing on how specific phenotypic traits influence medication bioavailability, efficacy, titration curves and predisposition for adverse events. This knowledge demonstrates that the integration of phenotypic traits with individual biomarkers can predict signs, signals, and symptoms of an oncoming adverse event in a clinical trial before it occurs or at a point where harm can be prevented. This harm aversion is a function of calculating normative ranges at the level of the traits that compose the participant's phenotype. By computing normative ranges for specific phenotypes, cases where a biomarker changes as a function of the study medication will have specificity to the individual participant, signaling a potentially oncoming adverse event in a way that broad whole population normal ranges on biomarkers cannot. By observing that a participant has a biomarker that is statistically atypical for the phenotypic population, the opportunity to pre-emptively divert an adverse event is more probable.

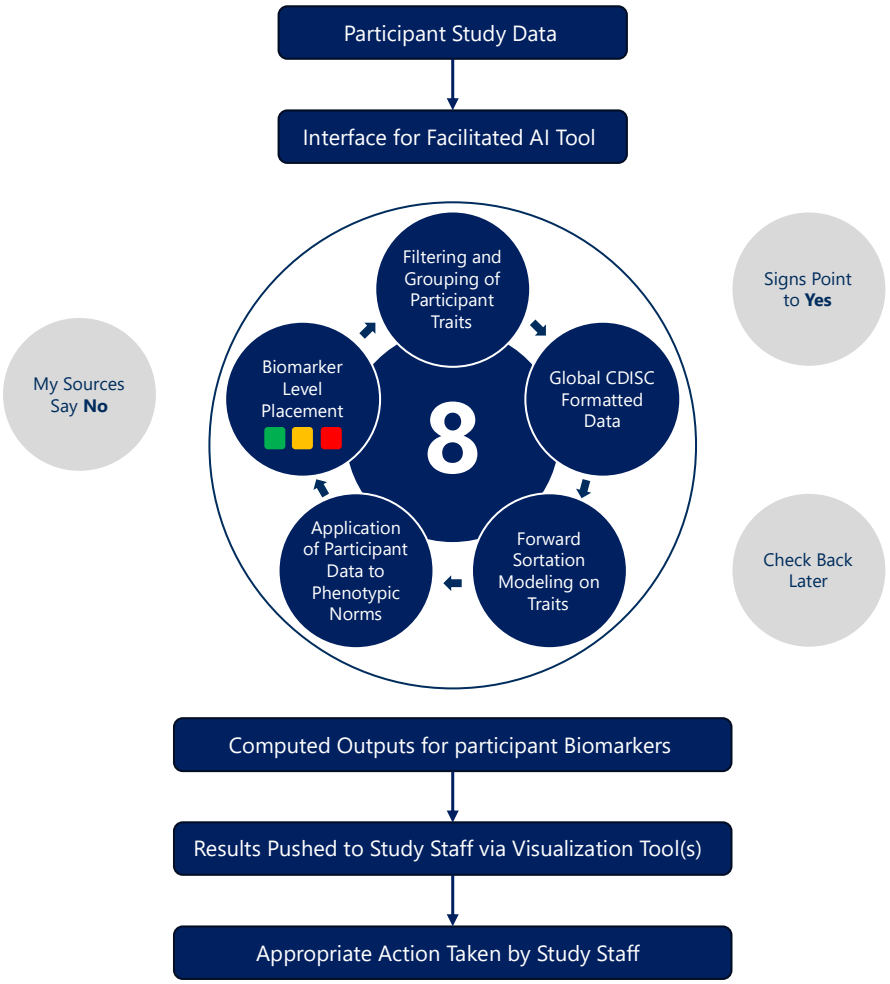
The application of participant phenotypic traits into tools that alert clinical study staff to potentially oncoming adverse events is achievable due to industry standard data collection, standardization, storage, harmonization and transmission pipelines. This allows for very large quantities of data that describe the phenotypic traits and lab values of countless research participants. Modern secure cloud computing and directed artificial intelligence technologies pave a path for applying these data to methodologies that automatically define phenotypic groups and biomarker levels that are normalized to those specific phenotypic groups. Incoming data can then be compared against those group norms and the calculated values can be pushed to information technology tools used by clinical study staff. Such artificial intelligence facilitated application of these data can be trained to spot

cases where biomarker signals demonstrate levels atypical for specific persons and issue the trial staff cautions and warnings of potential adverse events – before such an adverse event occurs.

ARTIFICIAL INTELLIGENCE FACILITATION

This tool will employ artificial intelligence (AI) to carry out the appraisal of data against themselves and data found within scholarly and peer reviewed sources that are accessible on the internet. The results will then be applied against these data. The processes within the AI engine beyond those defined in the tool are not static. The AI engine is constantly learning and evolving. Upon completion, the tool will be like the Magic Eight Ball. As inputs are passed to it, the tool predicts the future with processes beyond the knowledge of the user.

ARTIFICIAL INTELLIGENCE VISUAL



TOOL DESIGN

The proposed tool will have six major components:

1. Capture of data from participating industry and regulatory partners to populate a massive repository of phenotype traits and associated biomarker metrics.

2. Processing of records to ensure that all data are semantically and structurally equivalent across datasets. Here data will be restructured, reorganized, grouped, filtered for categorically false entries, and drop datapoints or records that cannot be reconciled.

3. Processed data from across submitting participants will now be assembled into a unified data structure (The Repository) with data from across the globe that can be used together.

*** Note:** The specific phenotypic traits of participants will be matched to those in the repository and data stored will be at the grouped by level. This automatically deidentifies any specific study participant to overcome privacy requirements.

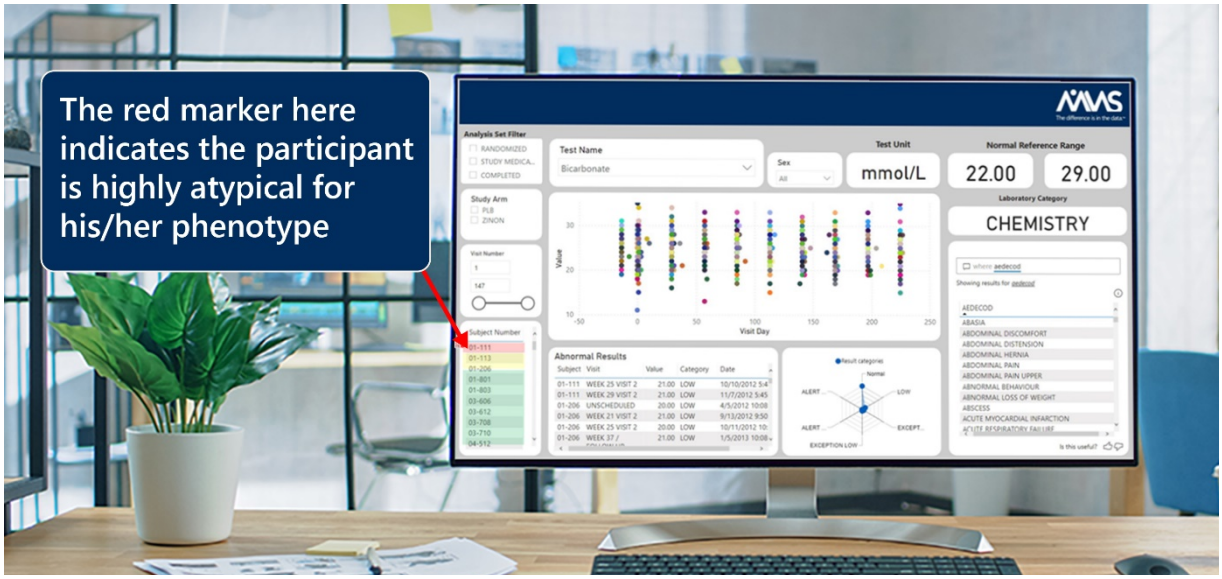
4. Data from the repository will now interact with AI tools under defined logic-based parameters.
   4a. These parameters will instruct the AI engine to group the permutations of phenotypic traits and then compute and store metrics on biomarkers for these same grouped permutations.

   4b. The AI tools will, in parallel, look to defined scholarly resources (ex. Cochran Reviews and high impact factor journal articles found within PubMed) to define and store adverse events associated with specific biomarkers that exceed or precede a statistically normal range.
   4c. Computed data and associated adverse events for biomarkers will be stored in tables for downstream application

5. Incoming data from active clinical trials will be securely joined with the AI created phenotype by biomarker ranges table(s). AI will now scan all the biomarker levels for each participant based on phenotype and define the participant as having:
   5a. No observed risk for a predictable adverse event
   5b. Elevated risk for a predictable adverse event
   5c. High risk for a predictable adverse event

The tool will push the biomarkers with elevated risk and high-risk biomarkers and associated potential adverse events associated with these risks to custom patient safety dashboards as supplied to clinical staff, primary investigators, and medical consultants on the project. Note that risks identified by this tool are evaluated by clinical caregivers who will make the final determination of how to proceed with patient care.

POTENTIAL STUDY STAFF FACING DISPLAY EXAMPLE

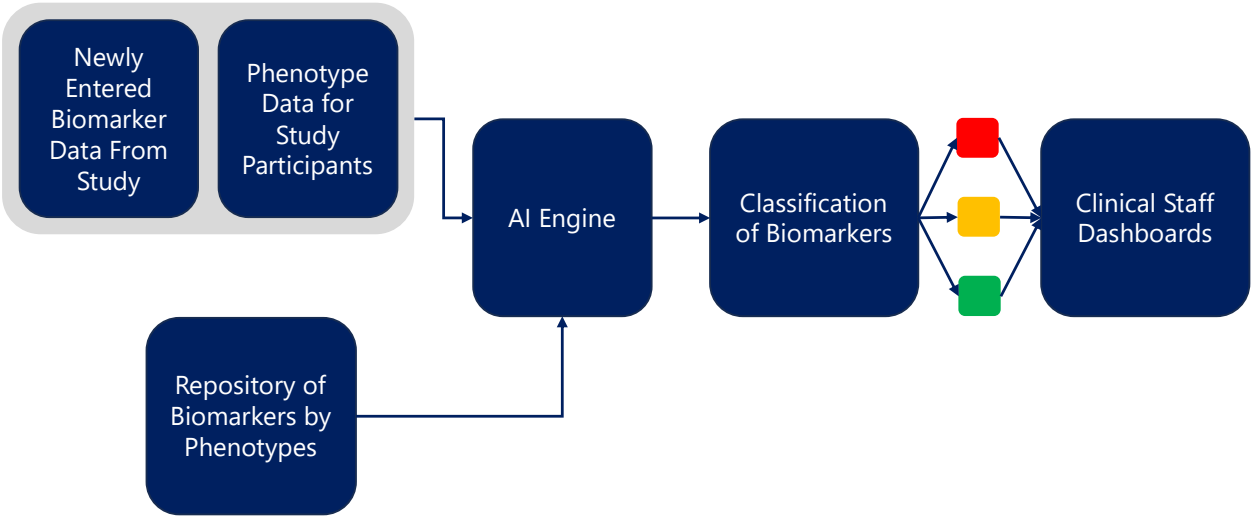


TOOL USAGE

As a high-level summary, the integration of data from the broad repository of prior study data will be passed into AI when new participant data is input. The AI will define the specific biomarkers for each participant and classify them as within a **normal range** (lacking in evidence for a potential upcoming adverse event), at an **elevated risk** for an upcoming adverse event (where a level is outside of a normal range but here the difference can be

considered borderline) and **high risk** when a level is highly outside of norms and or other evidence suggests a high probability for an upcoming adverse event. These levels of risk for the biomarker and that participant will populate outputs that provide the specifics of these differences to the clinical staff but also with clear color coding of **Green**, **Yellow**, and **Red** respectively. These easy to read and simple to understand flags for the data will be set to immediately trigger notifications in dashboards and other alerts as soon as newly received data are processed. These tools would be completely automatic for the clinical staff and require no programming or any additional software learning. High risk cases would be pushed to the top of the display and elevated risk cases beneath those.

TOOL PROCESS FLOW



EXAMPLE CLINICAL CASE

Participant enrolls in trial for a new medication

Participant provides demographic, medical history, concomitant medication and other applicable phenotypic data In consent and enrollment process

Participant provided with experimental medication

Biosample collected from participant and processed at laboratory

Lab findings sent to data management/data science
→ Lab data automatically sent to the proposed safety tool suite

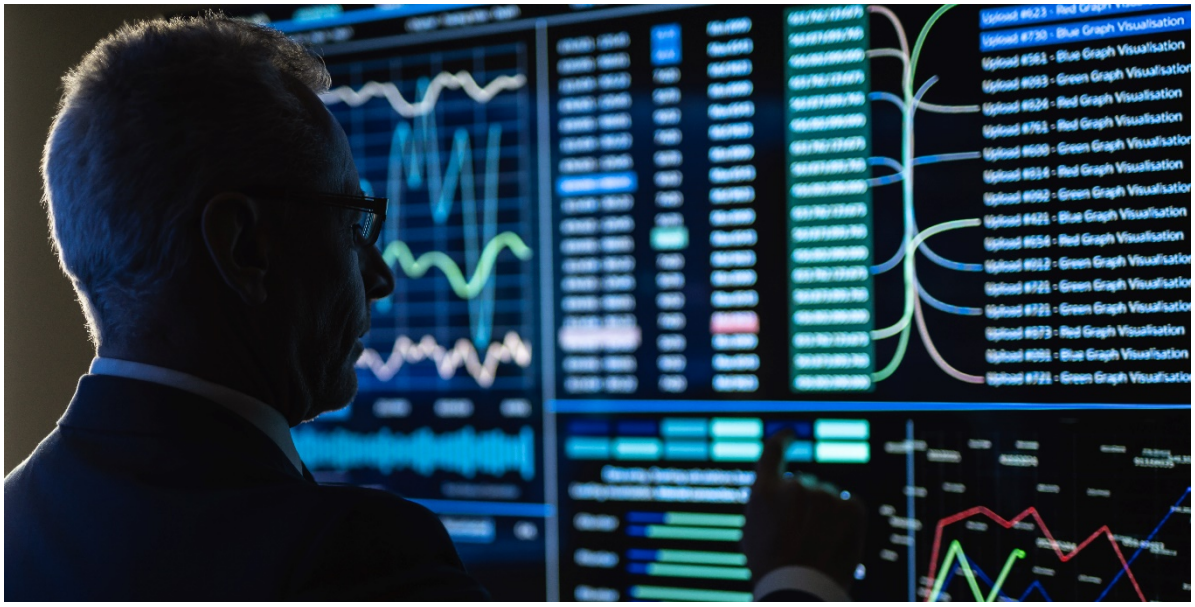
Phenotype data from participant matched with grouped data in repository and biomarker levels appraised against measures from historical control participants with the same phenotype
→ Levels from the specific biomarkers for this specific participant are defined in the Green, Yellow and Red categories

Findings from the safety tool suite are pushed to the clinical staff administering the research trial

Easily distinguished color-coded indicators on lab levels are presented to the research trial staff in dashboards, automatic text alerts or other notification methods based on assigned parameters.

The research staff in conjunction with medical reviewers, scientists and others providing expert advice can act on findings seen in the provided alerts.

Participant provided medical treatment, withdrawn from study, provided with additional monitoring or continues in trial following expert appraisal of data



CONCLUSION

The interaction between within participant traits and the potential for an adverse event resulting from a novel medication is a known challenge in clinical trials. The availability of a fully developed suite of data tools that is available to anyone using CDISC standardized data is the solution to this known issue. By having a team of international experts on clinical trial data, biometric characteristics, artificial intelligence in the biophysical space and computer scientists working together, high quality tools for this application can be developed. Without exaggeration, these tools have the power to save lives. By using data that are already collected about clinical trial participants and passing those data through these tools, important information on how the study drug is interacting with a participant based of a phenotype, critical details on how that drug is influencing the participant's physiology can be known even before other signs and symptoms can be observed otherwise. By having atypical biomarker metrics that are specific to a participant's phenotype, study staff will be provided with critical data that signals a potentially oncoming threat to a participant's health before it can be seen otherwise. Similarly, in cases where an adverse event due to a study medication does occur, the alerts from this tool have the power to lessen the influence on that participant's health by signalling it early and allowing for more rapid intervention in at least some cases. These examples of how such a tool will be used to provide enhanced participant safety in a clinical trial illustrate the need for these proposed tools to be developed.

Beyond the primary goal of reducing the risk participants have when enrolling in a clinical trial, this suite of tools will allow for many associated benefits.

A. This tool will allow for trait identification and interaction effects with respect to the safety and efficacy in ways that improve statistical analysis methodologies in a new drug application. The specific data produced by the facilitated AI processes will allow data scientists and statisticians to validate within participant statistical norms, with specificity not currently available to apply to statistical analyses.

B. Appraisal of frequency of events in a cohort sample with the specificity of these data could be used by reviewers to identify suspicious data. Characteristics within biomarkers that demonstrate too much or too little variation across phenotypic groups could be used to signal:

i. process errors in data collection,
ii. Faults in study methodology,
iii. Mechanical error or bias in test equipment
iv. Intentional misrepresentation of data to depict a desired effect.

Each of these issues is known to be not only a threat to the validity of any clinical research trial but also

to the public more broadly.

C. The enhanced and rapid safety monitoring will allow those conducting a clinical trial to reduce liabilities. This effect could be inferred to have many fiscal benefits across the clinical research trials portion of the pharmaceutical industry. It is foreseeable that such an extra level of appraisal at the phenotypic level during the clinical trial and in the analyses of data in the new drug application may also add security to regulators appraising a new medication.

D. Less represented populations could now be eligible for trial participation and have a reduced potential for an adverse event. Application of phenotypic trait by biomarker metrics monitoring in clinical trial methodology will allow alternative sample power calculation methods that no longer must exclude smaller sub-cohorts due to concerns about drug to phenotype interaction unknowns. By enrolling a less homogenous participant cohort, there are many diversity, equity, and inclusion benefits. These include the potential for identifying phenotype loaded risks for adverse events that could later harm populations not included in clinical trials. Fostering trust in populations that have historical grievances on how pharmaceutical safety ignored their own population. The potential for innovation based on unconsidered drug to phenotypic trait data may provide a path to new breakthroughs.

When reflecting on the potential for the personal safety alone, it is intuitive that such a tool needs to be developed. Considering that the data that would be used to populate the system that data would be appraised against are in a standardized format that are available to be integrated, this tool is a completely viable product to be developed. The precise technologies and methodologies that will be used to power the facilitated AI engine required will require a team of dedicated experts to develop; however, tools used in other markets appear to use similar core principles and could be applied here to facilitate development. Not only would such an interdisciplinary team of experts lead to a cutting-edge suite of safety tools, but it would also foster collaboration across the industry, this would involve work aligned with PHUSE real world data, AI and machine leaning, patient safety, open source programming tools and leadership. Such an integrated group of contributors would also facilitate the develop a tool that could be a public example of transparent risk-based monitoring. Ultimately, when we consider that this tool has such a clear opportunity to protect study participants from scenarios that can even include death, the case for developing this tool is clear.

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