

9. Automations



This paper will intentionally focus on automation technologies as these are mature and their applicability to CDM is immediate. As covered in the previous reflection paper, opportunities offered by emerging technologies have the potential to revolutionize clinical development and dramatically change CDM at its core¹. While the automation of many CDM activities is unavoidable, the future of CDM has never been so bright. In a world where people and intelligent machines will collaborate, CDM leaders need to take proactive steps and articulate a clear capability strategy toward CDS that considers all aspects: people, process, regulations, standards and technologies. Each organization’s CDS roadmap may depend on its data assets and technology maturity.

9.1 Emerging technologies driving automation

Before diving into automation, it is important to clarify the underlying technologies enabling the development of “artificially intelligent” applications and the differences between artificial intelligence (AI), robotic process automation (RPA), intelligent process automation (IPA) and other related technologies. Figure 5 shows the key components necessary to power CDM automations. These components have different roles to play and could be used either individually or combined to deliver the desired CDM automations. They start with basic process automation (i.e., RPA) and evolve toward the simulation of human cognitive behaviors such as reasoning and learning by machines (i.e., true AI). They collectively enable a wide range of opportunities for CDM that will impactfully transform our discipline toward CDS. CDM Leaders need to set a clear vision and roadmap to unleash this CDS potential.

Robotic Process Automation (RPA)	Intelligent Process Automation (IPA)	Natural Language Processing (NLP)	Natural Language Generation (NLG)	Machine Learning (ML)	Artificial Intelligence (AI)
Basic Automation of repetitive and predictable tasks	Advanced Automation of non-routine tasks	Language and text analysis	Generate text and voice	Pattern recognition	Human like behaviors Self optimization and Learning
No / simple decision making	Some decision making and problem solving	Knowledge gathering	Knowledge sharing	Prescriptive and predictive analysis	Deductive analysis

Fig 5. Technologies powering automations

First, **AI** is an evolving field and umbrella term which typically includes natural language processing (NLP), natural language generation (NLG), machine learning (ML) and computer vision (CV). It also includes intelligent process automation (IPA) which is the natural evolution of RPA. With IPA, robots can perform non-routine tasks requiring more complex problem solving.

RPA is process driven, meaning it focuses on process automation, whereas AI, which focuses on thinking and learning, is data driven. RPA is sometimes considered by some to be the simplest form of AI. The fact is that RPA solutions do not require problem solving and are at best using decision tree.

IPA combines both RPA and components of AI. IPA is often powered by ML and NPL which were both covered in the reflection paper Part 1¹. Smart IPA workflows monitor and track information exchanged between people and systems in real time, and ML empowers intelligent, rules-based decision making. NLG converts and interprets text/voice to allow human language-based communications.

9.2 Roadmap to the automation of data reviews

As an example to show the evolution of CDM to CDS, some CDM leaders foresee that AI will be driving the evolution of data review from traditional to supervised. The evolution may include 4 distinct steps:

- **Stage #1 – Automation of traditional reviews:** Data trends and anomalies will continue to be identified via edit checks, listings and dashboards. However simple and repetitive tasks will be automated with RPA (see Section 9.3 on RPA).
- **Stage #2 – Actionable reviews:** In this context, systems identify data trends and anomalies via ML-based automations (see Section 9.4 on IPA) and statistically based analytics to detect atypical data patterns¹⁷. The adoption of advanced analytics rose recently to support risk-based monitoring and has significant potential in reducing the need for complex and labor-intensive manual data trending.
- **Stage #3 – Guided reviews:** Guided review is the natural evolution of actionable cleaning. Once the automated detection of data trends and anomalies have matured, and when the volume of actions manually taken by CDS is meaningful, ML Tools will be able to learn from them and automate actions. In this first stage, CDS will review suggested actions prior to execution. NLG may also be implanted to automate the writing of queries.
- **Stage #4 – Supervised reviews:** In the end, systems will automatically detect and act. They will only escalate new scenarios to Clinical Data Scientists when they do not have enough knowledge to take a decision autonomously. In this context, Clinical Data Scientists will oversee the systems, support their training, and arbitrate complex data issues that systems cannot “judge”. They’ll oversee the entire ecosystem to prevent bias, privacy and ethical breaches.

As shown in figure 6, the value and more importantly the transformational impact of automation will grow as CDM evolves to CDS, from stage #1 to #4 automations. Stage #1 automation will mostly require very few of the technology components from figure 5. However, Stage #4 automation will be more complex and need the full power of all automation components combined.

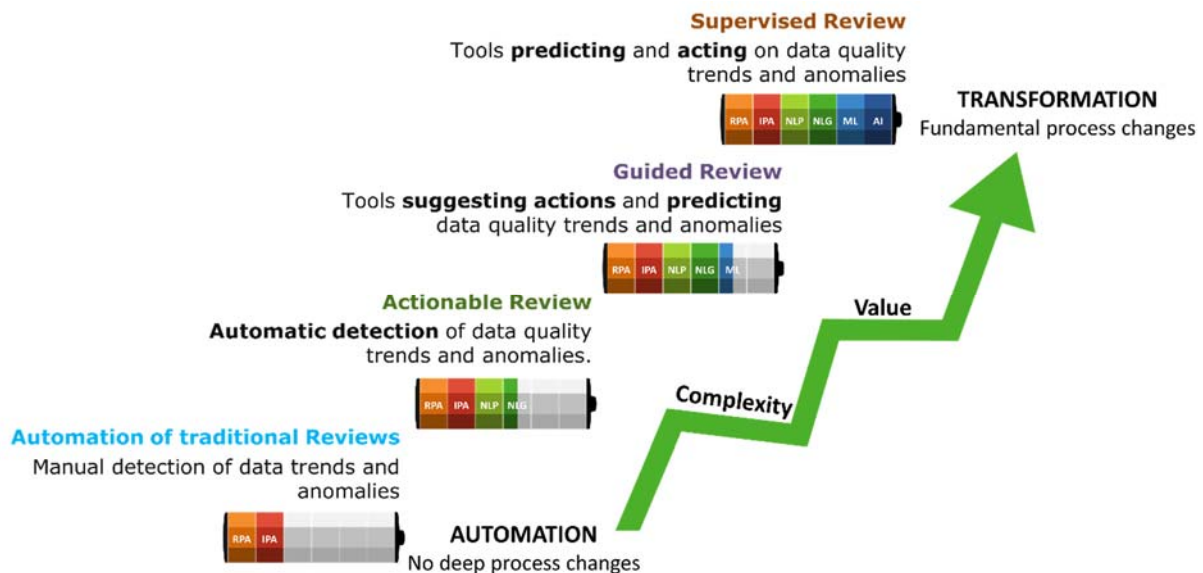


Fig 6. Evolution of data reviews powered by AI technologies

9.3 Robotic Process Automation

RPA is the simplest form of automation technology which is implemented through software applications, or robots, that perform predictable and routine tasks that do not require complex decision making. RPA is a mature technology which has been widely used across industries for years. It can mimic human interactions across multiple applications and is usually implemented to improve efficiency without the need to deeply change existing processes.

Typically, RPA applications take the form of a “bot”, which can be thought of as digital employees (e.g., Virtual Clinical Data Manager). Implementing RPAs helps reduce process time, increases throughput, enhances accuracy and frees up human employees by helping them to focus on the tasks that bring the most value back to the organization. To unlock its value, it is imperative to begin by setting a framework to educate all clinical research stakeholders and evaluate prospective opportunities for automation.



As a **first step**, organizations should establish an AI-focused team that is responsible for meeting the organization’s vision and delivering its high-level strategic roadmap. The team should be cross-functional, with representation from all roles supporting clinical studies as well as enabling functions (e.g., IT, finance, etc.). This team should be chartered and provided the means to deliver impactful business automations. Each automation must set clear objectives and measurable outcomes (e.g., cycle times / resources reduction, accuracy increase by X%, etc.).

The **second step** is to educate the team on AI principles and their scope of applicability. As previously mentioned, AI is a combination of capabilities that allow machines to replicate human decision-making and/or interactions. Each capability offers different opportunities and is associated with different levels of complexity. Once these different principles are clear, it is easier to strategize and focus on specific RPA opportunities.

The **third step** is to collect potential ideas for automation. There are many ways to collate ideas, however, onsite workshops focused within each business line can accelerate the process by bringing together functional SMEs to review ideas and opportunities in real time, and provide a forum for others to discuss and build on them. Each SME should be prepared to present a description of the automation and where it fits in the high-level process, including any potential changes that may be required to the process to enable the automation. For instance, data may need to be stored in a different location to accommodate the bot, or access to a data source might need to be opened to a different business group that was historically not considered. The business value should also be clearly articulated. The expected outcome of these sessions is not only to identify opportunities for automation, but to prioritize the opportunities for delivery and estimate potential time and/or cost efficiencies and cycle-time reductions.

The **fourth step** for successful RPA implementation is to establish clear short-term and long-term automation roadmap goals. After assembling and reviewing all of the automation use cases, the team should prioritize the projects with the highest alignment with the company’s strategic goals, and use those to set the foundation for how to implement AI/RPA with your department. As CDM review each idea, they can clearly define which components of the AI principles would be utilized to roll out the solution. Projects only requiring RPA capabilities, rather than those requiring hybrid solutions, should be

prioritized for easy and rapid implementation. Each project should be assigned a team lead, SMEs and project manager. The team should also align on a metric that will be reported out once the automation goes live and training/change management is in place to ensure full adoption of the new process. Once the organization has been trained on the RPA, it is important to track utilization of each bot to ensure the full value of the automation is truly realized. Low bot utilization could also point to issues with how it was programmed or implemented, and that should be addressed via programmed updates over time to ensure that the bots grow with the business process changes. As CDM optimizes and automates core processes, it must define target end-to-end processes and operational plans to ensure that opportunities are prioritized to enhance processes in lockstep with the company's technology strategy.

The **final step** is to build a sustainable automation development process, or an RPA Factory. This means developing a process with input from all relevant stakeholders, testing the process and validating each bot to ensure the workflow is correct and efficient. Potential areas of automation could include:

- Serious adverse event reconciliation
- Automated clean patient tracking
- Auto-generation of edit check specifications
- Automated loading of 3rd party data
- Automation of clinical data reviews
- Analysis and reporting system process triggers (scheduler)
- Automated quality review

Once a stable process has been developed, organizations should establish a global governance model to ensure alignment on prioritization and the funding of future automations.

9.4 Intelligent Process Automation



One large sponsor organization conducted a 'hackathon' which focused on the intelligent automation of the query management process. It involved the review of thousands of clinical data points to determine if a data discrepancy should be queried with a site. Many studies have thousands of manual queries raised over a long period of time (lasting from several months to many years). CDM must reconcile data across several CRFs by reviewing audit trails manually to determine if a query must be raised or not.

The hypothesis of the hackathon was that smart machines can learn from historical data by associating multiple clinical datapoints to specific manual queries, and establish clear data to query association patterns. When a similar pattern is presented to this trained model, the expectation was that it could predict discrepancies and, possibly, raise queries.

Data from several historical studies from various EDC systems were provided to the hackathon participants in a secure cloud environment. The studies had multiple data standards and millions of clinical data points. ML models were developed by four companies using various state-of-the-art techniques including deep learning. Vendors were evaluated on various aspects including innovation, accuracy and their ability to scale to a production solution. The outcome was successful in establishing a method for intelligent machines to perform CDM activities and proving that the hypothesis was correct. A semi-supervised learning approach was determined as the most successful method. Some labeled data were provided for supervised machine training by CDM SMEs and combined with an unsupervised learning algorithm where machines predicted similar patterns through observations.

As a next step beyond the hackathon, the selected ML will be trained with data beyond those provided for the hackathon to ensure strong accuracy and consistency of the predictions for critical data domains such as adverse events (AEs) and concomitant medications. Once perfected, the model could be operationalized by integrating it directly into EDC or intelligent CDMS systems. At this stage, these models can reliably detect complex cross-panel data discrepancies and save valuable time. The ‘human in the loop’ method will enable CDM to review all predictions, determine if they are correct, and later automate the generation of queries.

Natural language generation (NLG) will ultimately evolve to the point where machines can compose queries depending on the discrepancy context. The approach of using historical discrepancies and their associated queries will only train machines on known patterns. Future work to expand this use case to inference and clinical reasoning can move the AI needle more toward a CDS. For example, could machines detect AEs that are not reported? Can we take a subject holistically, analyze and reason whether a concomitant medication should have been taken when there was a reported AE etc.

Overtime, the model learnings from other clinical studies and SMEs will expand the horizons of AI and CDS. The technology can look across TAs, identify more complex patterns and adapt over time, while humans will assess machine inferences and provide invaluable feedback. In this context, computers and humans working together will make better predictions than either could do on their own.

Lastly, to successfully unleash the potential of AI-based automations, people will need to validate that this method is reliable, and that the IPA-based bot is a dependable ‘digital assistant’ that interacts with employees and partners to make important decisions. If an AI application is not well designed and managed, it may ‘misbehave’, with significant quality and ethical ramifications. These could range from damaged site relationships, negative impacts on patient safety and trial reliability, to missteps in drug manufacturing that affect quality and discriminatory decisions that elicit regulatory scrutiny.

Organizations need to consider establishing AI governance to build transparency and trust¹⁸. We should also consider ethical aspects, including bias that could potentially be introduced from data.

9.5 Considerations for the validation of ML based solutions

Validation of new ML Based solutions goes beyond the healthcare industry and has been extensively discussed in the literature¹⁹. Good practices recommend the use of three independent datasets in the development and validation of a new ML based solution. A model is trained on a specific dataset called the **training set** and is further optimized on an independent dataset, the **development set**. This optimization is an iterative process where the model parameters are tuned at each iteration to maximize specific performance criteria. This step is critical to ensure that models can generalize to new data while maintaining sufficiently high levels of performance. Finally, the performance of the optimized model is assessed on a third dataset, **the test set**. This step ensures that the validation of the model is performed independently from the model building process and that performances are not over-estimated.

Stakeholders need to play a key role in the definition of performance criteria and need to be trained in properly interpreting those metrics. This will leverage their power in making informed decisions regarding the release of new ML based solutions in a production environment. As an example, the accuracy, i.e., the ratio of the number of correct predictions to the total number of input samples, is a common performance criterion use to optimize ML solutions. However, the optimization of this unique

criterion may fail to produce models that are relevant for specific clinical use cases. Let us consider the optimization of a ML based solution, trained on the overall US population, to detect patients that will develop a rare disease. The US population is an unbalanced training set where the number of subjects with the disease (positive cases) is much lower than the number of subjects without the disease (negative cases). The optimization of the accuracy criterion alone in that setting would likely favor the detection of negative cases at the cost of missing true positive cases.

Once the model is released to production, several factors can lead to the degradation of its performance over time including a modification of the user's behavior or to the input data. A monitoring process should be put in place to actively assess the model performance over time and trigger specific actions when the model performance drops below a predefined threshold. These actions include the training and optimization of the model on new datasets and adaptation of the model architecture.