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AstraZeneca Early Clinical Biometrics Journey into Integrated Clinical Data Environment

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ABSTRACT

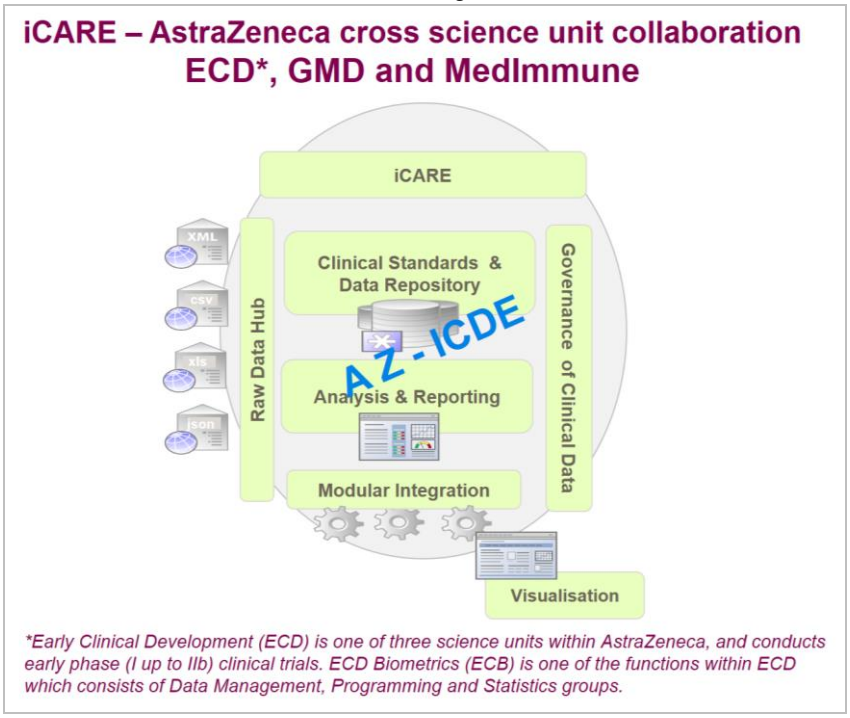
Managing and implementing a new system in any company can be a huge challenge, and embracing the new way of working is even a bigger challenge. In 2017 a single clinical trial data repository, analysis and reporting environment, entimICE-AZ, was rolled out to biometrics users across all science units within AstraZeneca (AZ). It replaced many legacy analysis and reporting platforms for clinical trial patient-level data, aiming to be the "single source of truth". The roll out of entimICE-AZ was a significant change in the way AZ Early Clinical Development (ECD) Biometrics team works and embracing the new system was key for a successful roll out. We believe that this paper will be an inspiring story for industry partners who are thinking about their move into integrated clinical environment. In this paper, AZ ECD journey into the implementation of entimICE-AZ, challenges encountered, lessons learnt and next steps are shared.

INTRODUCTION

Historically, AstraZeneca had been using different systems to store clinical trial study data and to deliver Analysis and Reporting (A&R) across its early and late phase science units. In 2014 the Integrated Clinical Analysis and Reporting Environment (iCARE) programme was launched to support the implementation of a single clinical data repository across AstraZeneca science units, offering a new A&R environment for clinical data, with standardised end to end process for the delivery submission ready data.

iCARE (Figure 1) delivered a single system solution, entimICE-AZ, in 2016, which replaced all legacy systems for Data Management (DM) and A&R activities. It was a collaborative effort across the science units to deliver the programme and to develop Standard Operating Procedure (SOP), guidance and processes to bring simplifications and efficiencies. The remaining of this paper will refer AstraZeneca entimICE-AZ platform as AstraZeneca Integrated Clinical Data Environment (AZ-ICDE).

Figure 1: iCARE Programme and AZ-ICDE – a collaboration among AstraZeneca science units.



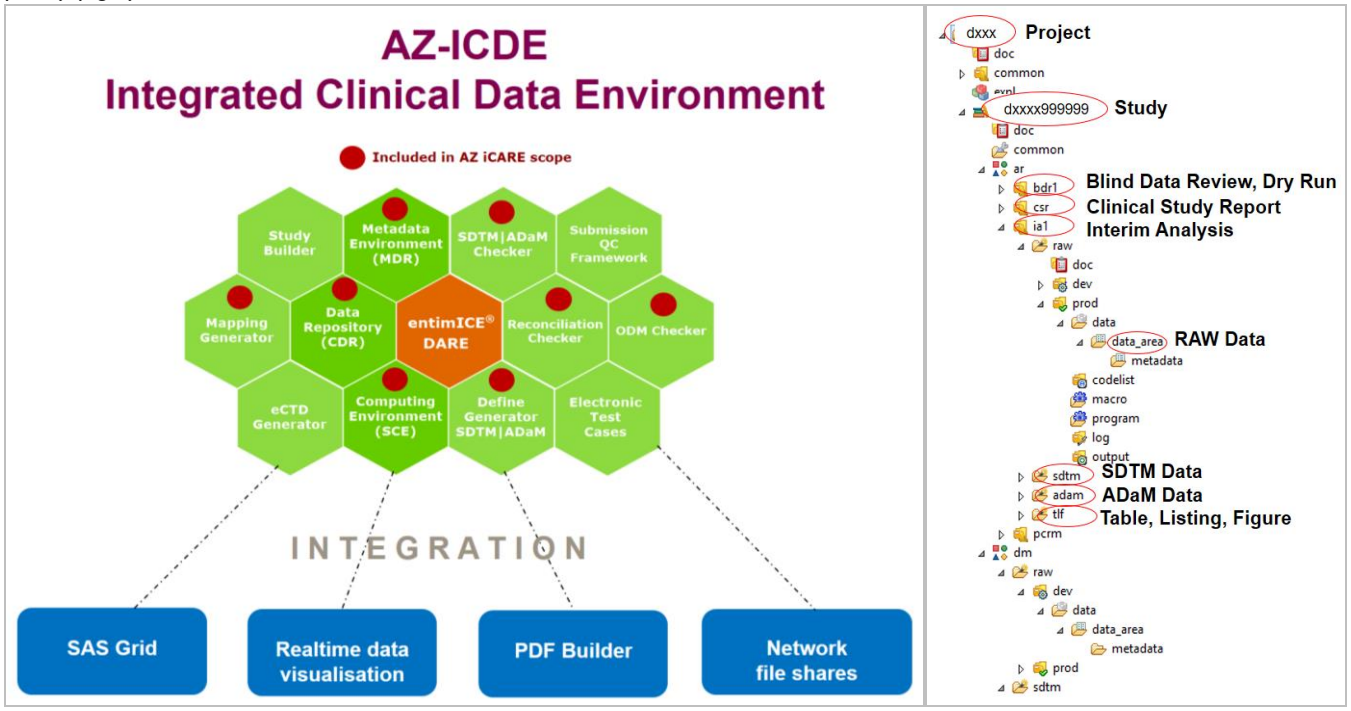
The rollout of AZ-ICDE also allowed us to migrate legacy studies, create clear data flows from our external vendors and partners, integrate with other systems to utilise metadata and act as a regulatory environment for clinical data alongside electronic Trial Master File (eTMF). ECD has been a key contributor to the iCARE Programme since 2014. In April 2017 we rolled the new system out to all Biometrics in Early Clinical Development.

The implementation journey has not always been a smooth one and there have been many challenges along the way, learning the new system, new processes, additional resources for support, training, data migration and embracing the new system by end-users. The next section provides a brief overview of the AZ-ICDE system. The remaining of the paper takes readers through the implementation journey based on AstraZeneca Early Clinical Biometrics experience, challenges encountered, lessons learnt, and the key recommendations for deploying a new A&R system.

WHAT IS AZ-ICDE?

AZ-ICDE is a clinical study data storage and analysis reporting environment (Figure 2). This is a modular system developed by Entimo AG (Berlin, Germany) and has been configured and hosted for AstraZeneca by the implementation vendor nnIT (Søborg, Denmark). Key modules of the system include clinical data storage, data standards, analysis and reporting. The system has also been integrated with other AstraZeneca systems, such as the SAS® Grid system, AZ internal realtime data visualisation tool, network file shares etc.

Figure 2: AZ-ICDE system modules (left) and a typical project/study hierarchy, also referred to as Master Transfer Structure (MTS) (right).



Key characteristics of the AZ-ICDE system include:

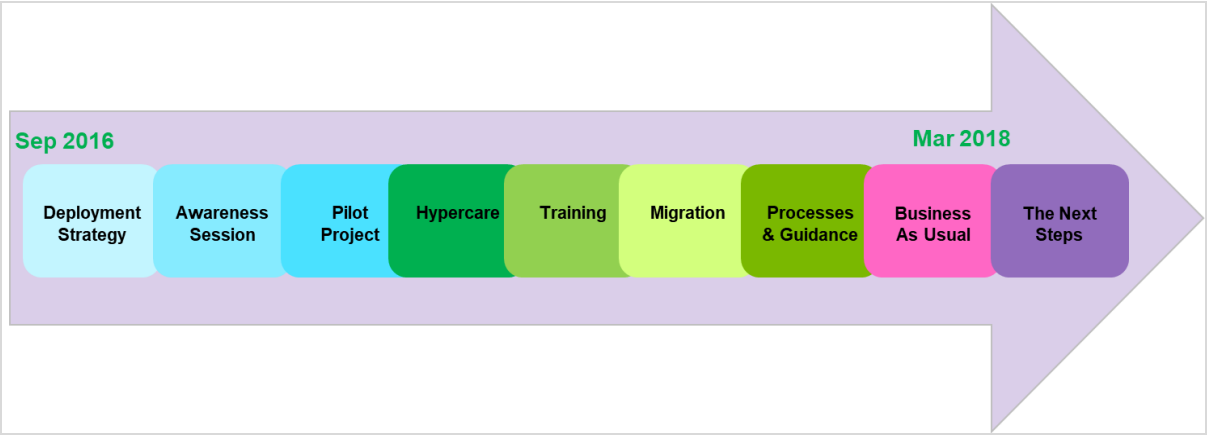
- Data and Metadata Repository
  - Store and manage data (RAW, SDTM, ADaM, etc.) and metadata.
  - Develop and provide data standards.
- Computing Environment
  - Develop programs for data transformation and analysis using SAS, R, S-PLUS.
  - Produce final analysis outputs and reports, i.e. Tables, Figures and Listings (TFLs).
- Secure Environment
  - Provide governance.
  - Control access, structures and workflows.
- Automatic Traceability
  - Version control.
  - Audit history and traceability.

The system has been configured for AstraZeneca to allow for different levels of user access, which are managed by various roles within the system. All project/study folders are created by following a controlled and consistent structure governed by SOPs and guidance, but also allows for flexibility when required. Various reports can be generated to view summary/detail information on objects, including metrics. The system is highly configurable, additional system modules, functionalities and reports can be integrated as required.

ECD JOURNEY INTO AZ-ICDE IMPLEMENTATION

The following sections focus on key milestones that we went through for a successful implementation of AZ-ICDE (Figure 3). Each section will outline the background and rational for the activity including any challenges and lessons learnt with the aim of sharing our experience. The implementation milestones below are outlined in chronological order as they were planned and deployed.

Figure 3: ECD AZ-ICDE implementation journey key milestones.



DEPLOYMENT STRATEGY

AZ-ICDE offers ECD a single repository for regulatory work in line with other science units. However early clinical development is explorative in nature and requires other tools beside those used for regulatory purposes. For example, a combination of Python and R for simulation and modelling activities is something that AZ-ICDE is not supporting. In addition, many of the legacy A&R environments were based on interactive SAS where network file shares were used for storage. Hence, the expectation from the user community was to have an equally flexible A&R environment for both regulatory and exploratory work. The AZ-ICDE system is furthermore hosted at a vendor's data centre, outside of the AstraZeneca IT network and firewalls, which created additional layers of integration complexity. In parallel to the AZ-ICDE implementation, the SAS Windows environment was upgraded to a global Unix SAS GRID platform with Enterprise Guide and SAS Studio as key program development tools. During the stakeholder discussions two aspects emerged as significant; a secure system with minimum interruption to drug project deliverables and an engaged end-user community. Although both aspects were equally critical, engaging end-user community was defined as key success factor for ECD based on previous experience.

For the ECD AZ-ICDE deployment team, the aim was therefore to have a flexible A&R platform for both regulatory and explorative work with guidance and process supporting one way of working. The ECD deployment team, proposed a project plan on how to implement AZ-ICDE together with SAS GRID and R, and this was endorsed by the ECD leadership team. We planned to execute the deployment activities in two phases to minimise impact due to these changes on drug project deliverables (Figure 4).

PHASE 1:

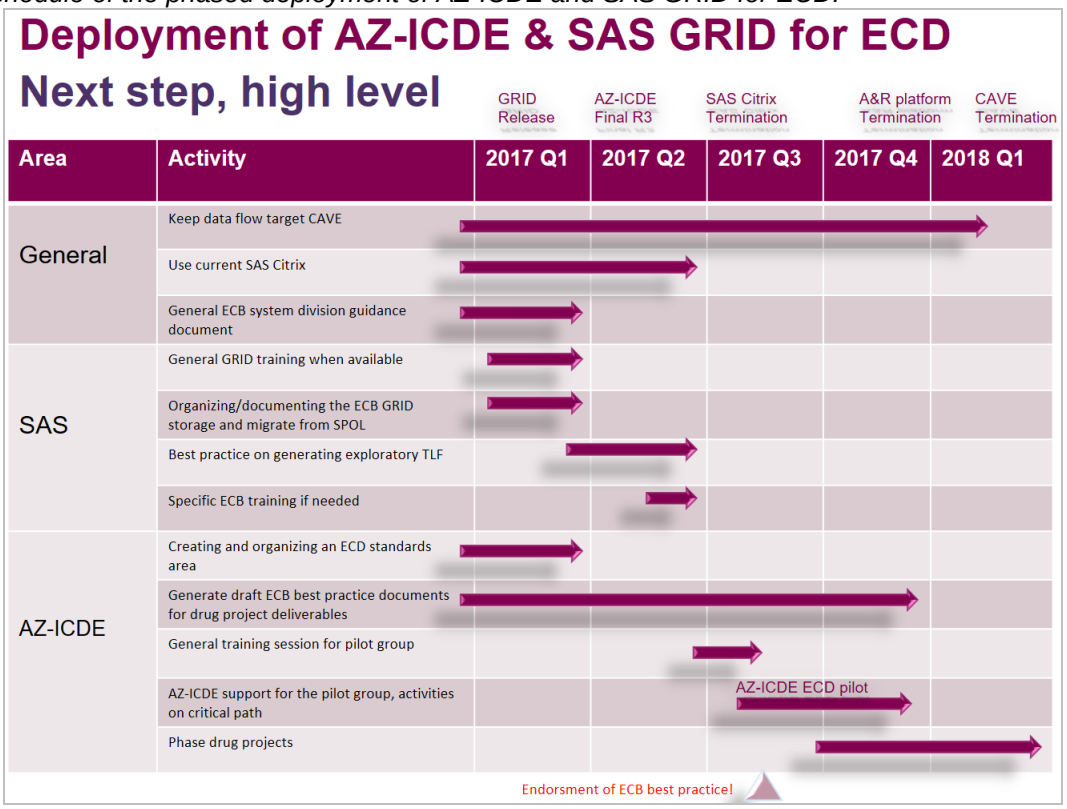
In phase one we migrated from the legacy SAS environment to a global SAS GRID solution. This allowed ECD to continue with the day-to-day drug project work using legacy network file shares and different legacy A&R systems, while giving them time to adapt to the new SAS environment. A group of early adopters from ECD were engaged in user requirement specifications, acceptance testing, development of guidance documents and training sessions with the ECD specific processes in mind. Global awareness sessions as well as specific SAS GRID training were delivered by the implementation vendor and the SAS training team during a 6-month period prior to the launch.

BENEFITS/LEARNINGS:

- Early Adopters help raise awareness and support as others adopted the new SAS environment. This change was well received by the end-user community since this brought a stable and upgraded SAS processing environment.
- It required minimum changes to existing SAS program codes e.g., changes to file path due to Operating System (OS) differences and provided low risk to project A&R deliverables and as a result no delays were seen.

- The SAS GRID and some legacy systems operated in parallel during the transition period due to drug project priorities allowing the shift to be more at individual level rather than functional level. Using multiple platforms within the same project introduced overhead in managing program codes and deliverables, and this is something that should be avoided in future deployment projects.
- Running two major changes in SAS environments in parallel was not optimal but more influenced by SAS licences renewal and the fragmented global SAS environments that required a refresh.

Figure 4: Schedule of the phased deployment of AZ-ICDE and SAS GRID for ECD.



PHASE 2:
The second phase of the plan was to introduce the new AZ-ICDE platform to the end-users. This started with awareness sessions and continued with early adopter users running pilot projects and specific tasks supported by dedicated deployment team.

AWARENESS SESSION
The aim of these sessions was to communicate a high-level overview of the proposed changes, how AZ-ICDE and SAS Grid would be used in combination, and to collect end-user feedback on the proposal. The core part of the sessions contained information on system functionalities, risks, benefits, training requirements and the "What's in it for me?" perspective to build excitement for the new system. Information covered were tailored for each respective function and included a section on how the end-users would be affected. We organised these meetings as face-to-face wherever possible to have the best end-user interactions. Some of the key information that we covered were:

- Roadmap and timelines for the changes
- Intended usage of the system, and a proposal for the division of activities between AZ-ICDE and SAS Grid.
- A set of focused questions to collect end-user feedback.

We wanted to gauge the level of understanding about the changes and to find out any end-user concerns about the proposal and help address them. Below are some example questions that we used to collect feedback from biometrics team.

- Would you agree to use AZ-ICDE for computing and for storing TFL outputs used for regulatory purposes, external presentations and internal decision making?
- What is the best platform to perform post-hoc and ad-hoc analyses on?
- What is the best way to share statistical outputs with the consumers?

We summarised all the feedback to improve the implementation and shared it with the team for any additional response. Below are some further comments from the teams around the deployment of the platform;

- Integration between AZ-ICDE & SAS Grid platforms and relevant processes are important.
- More information is needed clarifying distinction between AZ-ICDE and SAS Grid activities.
- More information is needed on SAS program development functionalities in AZ-ICDE.
- Need a solution to aid program development and transportation between SAS Grid and AZ-ICDE systems.
- A folder structure within AZ-ICDE project area is needed for project memory such as decisions made etc.

We analysed all the end-user comments and identified the following four key areas that required further work.

1) Why the changes are taking place with the SAS systems?
2) Why there are two SAS platforms (i.e., AZ-ICDE and SAS Grid) instead of only one?
3) How to clearly distinguish activities that should be performed on AZ-ICDE and SAS Grid?
4) SAS code development functionalities seem to be “insufficient” in AZ-ICDE compared to legacy SAS systems!

We organised follow-up awareness sessions to provide further clarifications on the first and second areas above. For the third and fourth areas, we had additional discussions with various end-users to understand the existing process before proposing a new guidance. One of the major end-user concerns was that AZ-ICDE seemed less flexible regarding program development functionalities compared to legacy SAS platform and SAS GRID. It was clear from user feedback that having program development tools, such as navigating through code sections easily, opening multiple datasets at a time for review, comparing table/listing/figure (TFL) outputs was important from user acceptance perspective. To address these user concerns a separate bespoke novel process named iGET, integrating SAS GRID and the AZ-ICDE using Webservices (a web-based technology to exchange data between systems), was created. The iGET workflow was also agreed to be used as a contingency process when the AZ-ICDE system was down.

In addition, we also wanted to imbed the platform change into the department and individual’s goals. This was achieved by formalising a set of soft skill objectives around the implementation.

- Plan additional time for project deliverables using the new system.
- Work actively to develop skills about the new system.
- Embrace positively the deployment of the new system.

BENEFITS/LEARNINGS:

- We learnt and modified as we progressed, tailoring to ECD end user’s needs.
- End-users felt listened to and that they could influence how the systems could best work for us all
- Setting measurable expectations from end-users, such as performance review goals, were useful
- Do not underestimate the need for user engagement and interactions which proved to be worthwhile since now in Business As Usual (BAU) with supportive processes and guidelines.

PILOT PROJECT

The aim of the pilot project (Figure 5) was to put a few low-risk drug projects through to the new A&R system to gain knowledge and experience about the platform. Lessons learnt from this pilot project were planned to be used for developing processes and has proven invaluable to our implementation.

We put together a plan for the pilot by selecting a set of candidate projects and tasks. We also proposed a resource allocation plan for the pilot projects which was endorsed by the leadership team. We used the following criteria to select pilot projects and tasks.

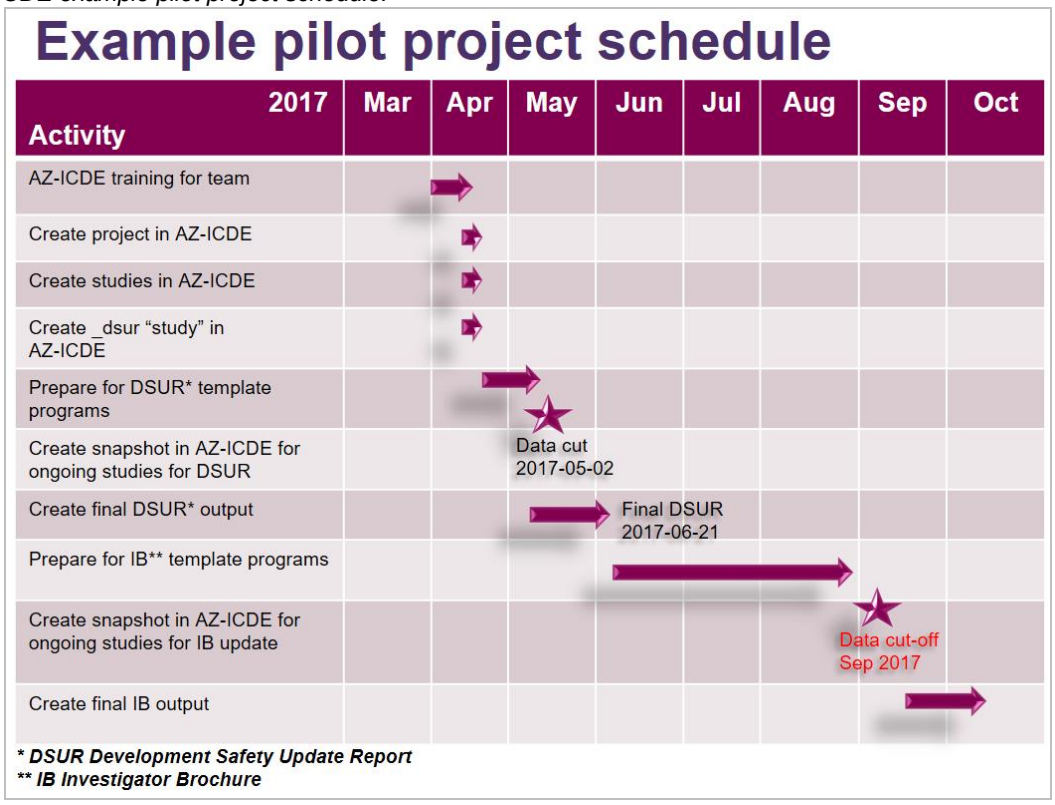
- Projects with regulatory deliverables (e.g., development safety update report and investigator brochure) with data cut off between April 2017 and October 2017.
- Low risk projects with non-critical timelines.
- Have a contingency plan e.g., use legacy A&R systems in case the new system failed.

We selected four drug projects for the pilot. This was a very challenging period for us given limited knowledge about the new system. The ECD deployment team supported the pilot projects and the key activities included were learning about the new system and associated processes, finding work around when a system functionality was not available as expected, collaborating with relevant ECD functions and AstraZeneca science units.

BENEFITS/LEARNINGS:

- The pilot activities helped us to gain an in-depth knowledge about the new system, to develop ECD processes and best practice guidance documents and to deliver additional training to support the biometrics team, and to plan and allocate resources for the next set of projects migrating into AZ-ICDE.
- Resources were stretched at times to meet project timelines.
- We shared lessons learnt from the pilot projects as part of communication and knowledge transfer.
- In addition, pilot project activities were also useful for us to align and simplify the mandatory AZ-ICDE training modules with biometrics functional roles.

Figure 5: AZ-ICDE example pilot project schedule.



HYPERCARE

The aim of the hypercare team was to provide end-user support and training on the new system (Figure 6). The team consisted of dedicated programming resources, and representatives from ECD implementation team and biometrics functions (i.e., Programming, Data Management and Statistics). The hypercare team put together a proposal for the implementation timelines, associated activities and required resources which was endorsed by the leadership team.

The hypercare team delivered the following key activities during the implementation.

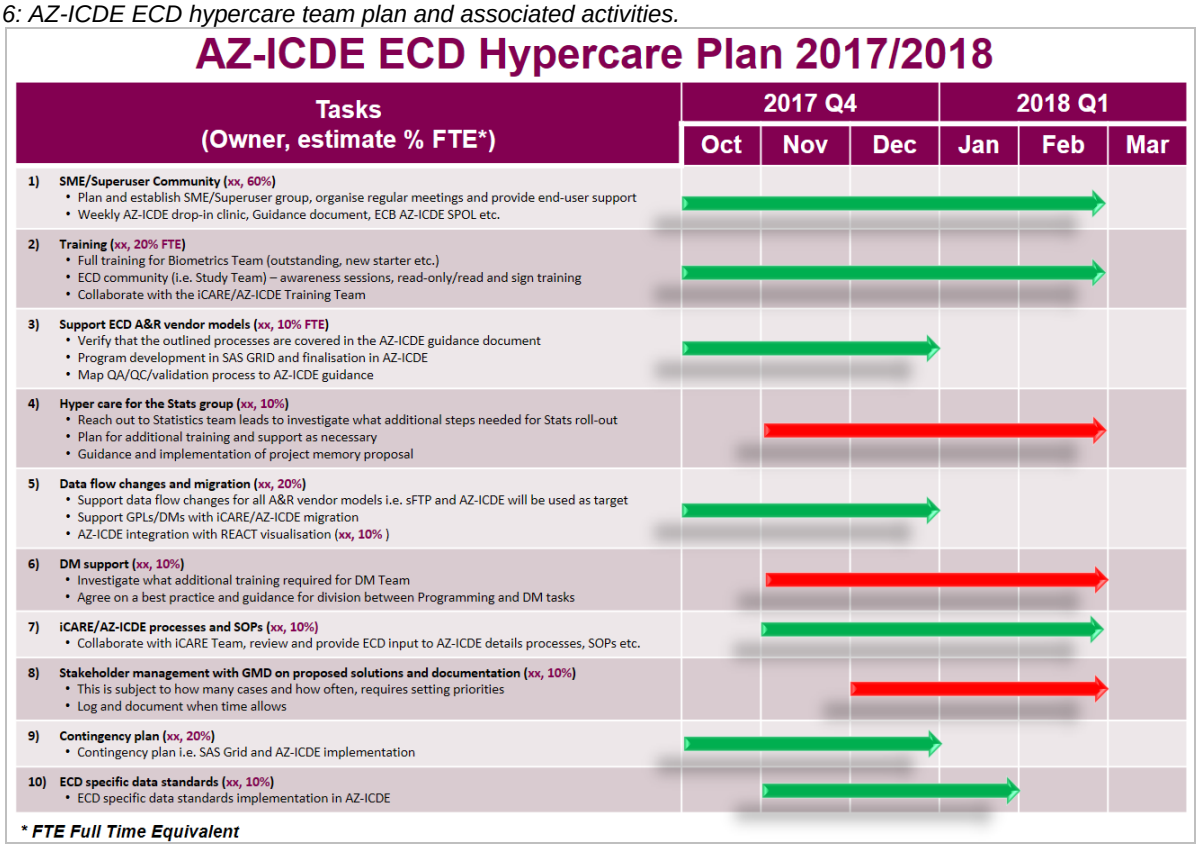
- End-user training and support
- Weekly support clinic including lessons learnt
- Regular communication via emails/newsletter and presentation in meetings

BENEFITS/LEARNINGS:

- Challenges due to limited experience and knowledge about the new system.
- The hypercare team had to be very innovative by continuously brainstorming new ideas on how to make the system a success, and how to support the end-user throughout the deployment with limited resources.
- Regular weekly meeting to discuss and plan hypercare team activities.
- Weekly ECD AZ-ICDE drop-in clinic and regular training/presentations throughout the implementation period to provide end-user support.
- One-to-one support to users as required.
- Learned from each other and from mistakes and continuously improved ways of working in the new system.

We believe that having a dedicated hypercare team supporting the implementation was one of the keys for our success.

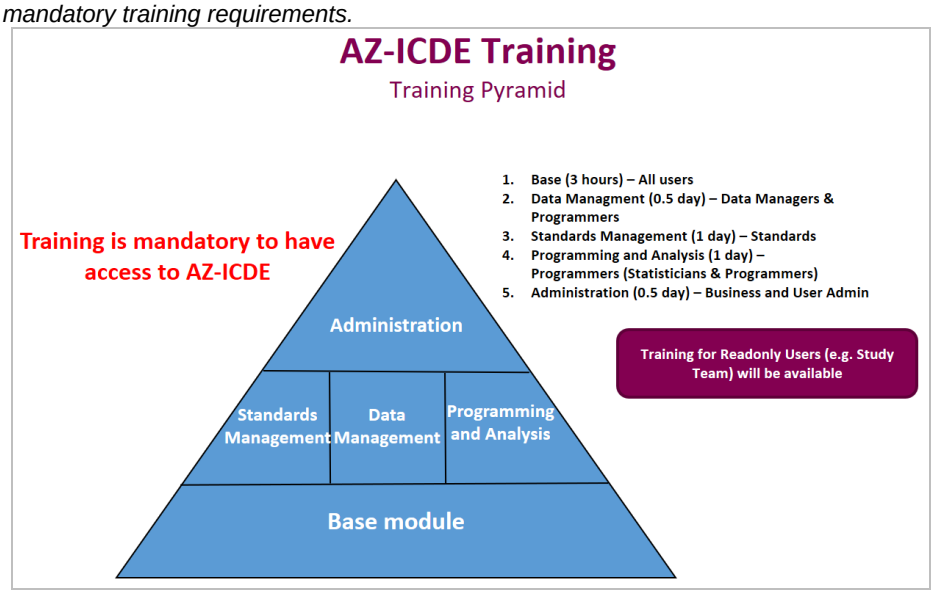
Figure 6: AZ-ICDE ECD hypercare team plan and associated activities.



TRAINING

Training was mandatory for all users to gain access to AZ-ICDE system (Figure 7). It was also a crucial part of building knowledge and efficiencies for the new platform. A role-based training matrix was in place to meet compliance and the training sessions were delivered by AstraZeneca AZ-ICDE training team. Training team consisted of trainers from science units. We delivered the training sessions via face-to-face and teleconference sessions. Due to logistical challenges, we then recorded some of the sessions and piloted with the aim of delivering all the future training as computer-based training via the company learning system. Within ECD we took the standard off the shelf training package and modified it to fit ECD needs, keeping core training in line with system access requirements, but streamlining it to ECD functional roles.

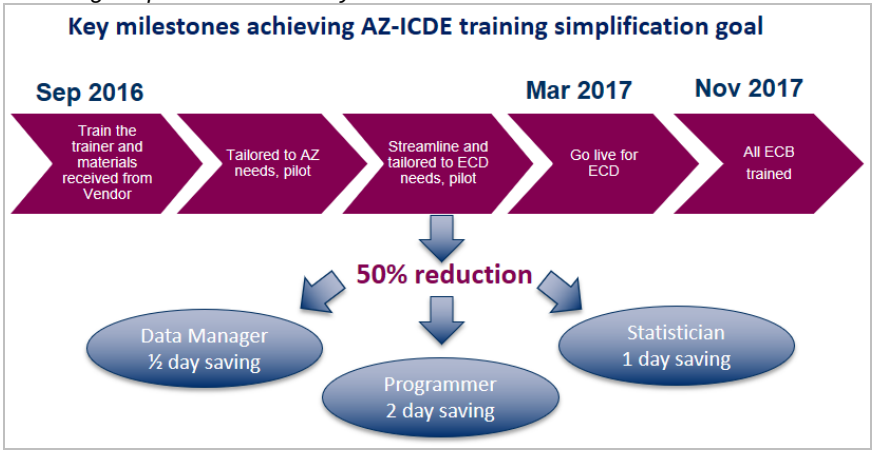
Figure 7: AZ-ICDE mandatory training requirements.



BENEFITS/LEARNINGS:

- The standard 'off-the-shelf' set of training materials and methods provided by implementation vendor did not fully align to ECD needs. We needed to get users up to speed quickly and in standardised way. We simplified the training methods and materials according to ECD biometrics functional roles by adapting the materials to different key roles and including relevant ECD processes, guidelines and examples.
- We streamlined the training courses (Figure 8) for sustainability by reducing the four 1-day sessions to four half-day sessions, saving 50% training time.
- The training simplification task also removed the need for travel costs, geographical dependencies, by making the sessions virtual though interactive training materials. This also phased out the need for instructor-led training by developing computer-based training for all AstraZeneca science units.

Figure 8: AZ-ICDE ECD training simplification summary.



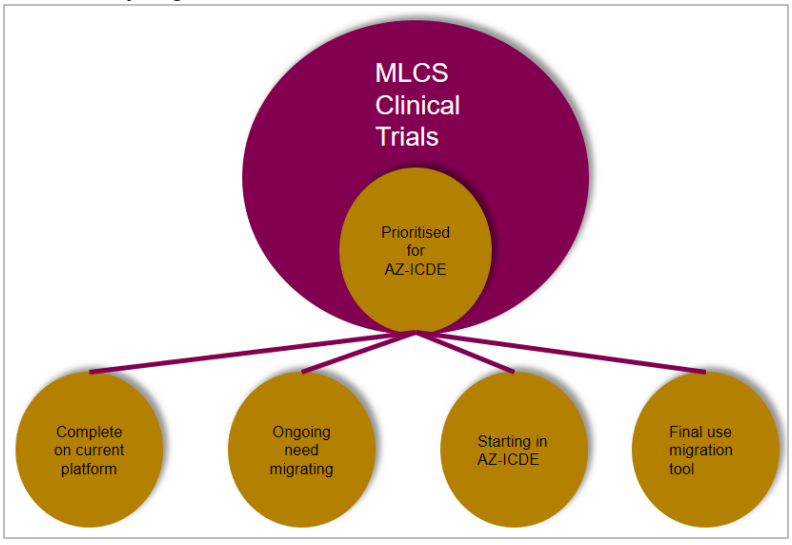
MIGRATION

Data migration from a legacy to a new system is a vital step for any system deployment project, and there is generally a high risk of failure. An organisation's productivity, with the new technology, is significantly reduced without a well-planned migration process in place. One root cause for the failure is usually due to underestimating the complexity and the amount of the work required with migration. It was realised early on by the iCARE team that an efficient migration process was a key success factor, and a dedicated migration workstream was formed to execute this.

There were four main objectives for the global migration workstream all supported by ECD

1) Consolidate historical data into a single central storage.
2) Upgrade all SAS data into 64-bit format.
3) Create a clear and an efficient migration process.
4) A plan to decommission legacy systems.

Figure 9: Priority classification for study migration.

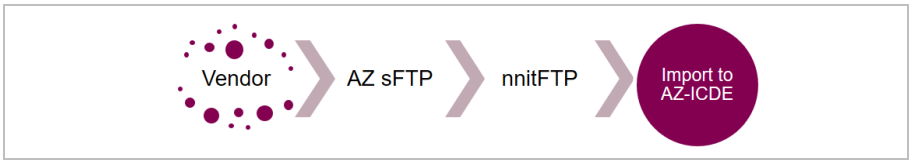


The first three objectives had to be accomplished prior to migration. It was also recognised by the team that not all studies and data needed to be migrated. This was mainly due to non-pivotal study, terminated drug project or divestment compound not being prioritized. It was important to have a single list of ranked studies across science units to manage both the migration process and timelines effectively. To manage this process within the science unit, we created a migration monitor spreadsheet using metadata from the master list of clinical trials for all ongoing and completed ECD studies. This tool was used to monitor timelines for regulatory project deliveries where migration was a preparation step using the new platform e.g., development safety update report, investigator's brochure, etc. We consulted biometrics leads for the respective projects before timelines for the migration were agreed and documented.

We classified the ongoing studies into three categories (Figure 9) based on efforts required for the migration. Studies with ongoing data transfer from external vendor to AZ system was regarded as the most complex. This part of the migration process was dealt separately as an additional activity with dedicated resources. The following two major changes influenced the dataflow between external vendors and AZ systems (Figure 10).

1) Legacy data transfer mechanism was replaced with a generic sFTP system to system service for all data e.g., SAS, TLF, images etc.
2) The files in the transfers had to be organised following the AZ-ICDE folder structure known as Master Transfer Structure (MTS) (Figure 2).

Figure 10: New data transfer method between AZ and external vendors.



Changes on the dataflow were communicated to vendors and related guidance were shared as well, relevant vendor handbooks were also updated. Using a generic MTS (Figure 2) for data transfer was part of a dataflow simplification process in AstraZeneca. The vendors had to make necessary changes in their systems to comply with AstraZeneca requirements for system to system sFTP transfer.

An in-house bespoke tool based on the Master List Of Clinical Studies (MLCS) metadata was developed by ECD to carry out the migration of completed studies. Since AZ-ICDE is based on a file storage rather than relational database structure, there was no need to transform, clean or validate datafiles for migration purposes. Therefore, the files were simply moved from the legacy to the new system by applying necessary file naming conventions automatically. The migration protocol was quality assured by the project programming leads before the actual migration was executed. The programming leads or delegates also made sure that the results were as expected on migration completion.

The migration process was regarded as a huge success. Some of the challenges encountered were limited resources, changes to dataflow for vendors, changes in requirements for some studies prior to migration execution, etc. Below are some key factors for successful migration based on AstraZeneca experience.

BENEFITS/LEARNINGS:

- Dedicated migration team working closely with IT department to develop generic cross platform solutions for consolidation of legacy file shares and Upgrade of all SAS data
- A bespoke migration process developed by ECD optimised for the business use cases
- Early identification of ongoing studies requiring migration support
- Collaboration with vendors on dataflow changes
- Contribution from drug project team with decision making such as prioritisation of studies for migration and Quality control of migration protocol

PROCESSES & GUIDANCE

The rollout of AZ-ICDE was a significant change in the way ECD Biometrics team worked with regulatory A&R deliverables and exploratory analyses. It was key to have all the relevant training, standard operating procedures, guidance and processes available to end-users for a successful implementation of the new system. It was equally important for the users to embrace the new system and to be part of the overall success.

BENEFITS/LEARNINGS:

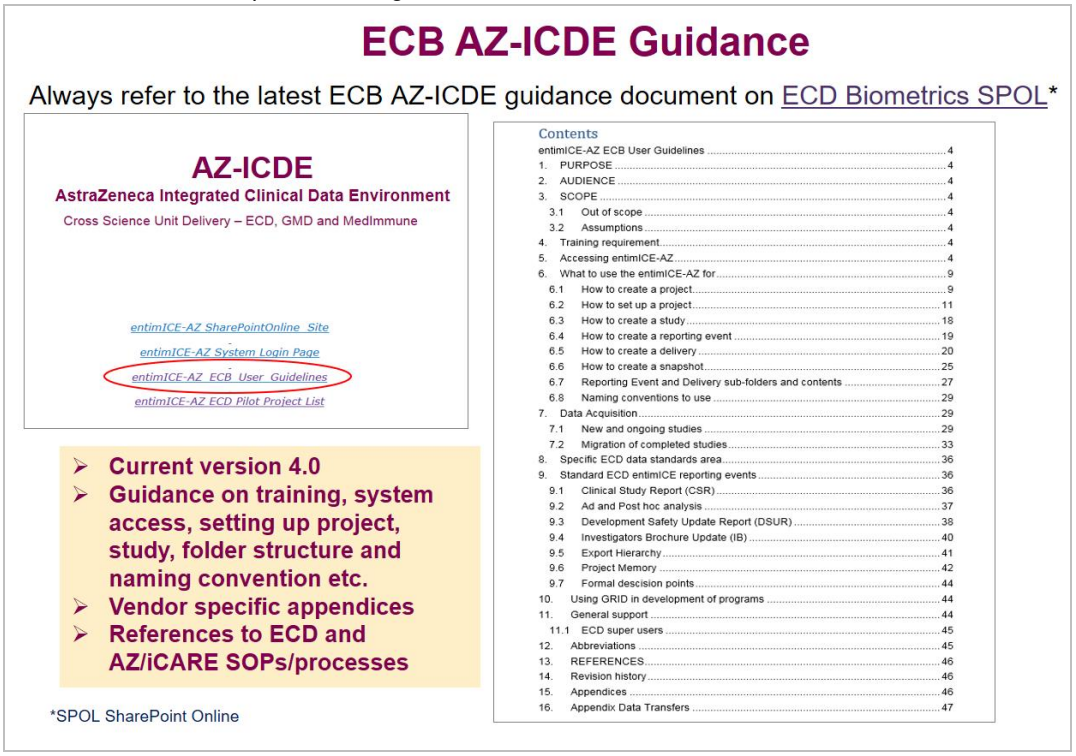
- There were AZ-ICDE standard operating procedures at the company level which enforced consistency across all science units. Some of the key processes standardised included security and access control, naming conventions, and data standards. The standard operating procedures were also designed to be flexible in certain areas to allow

science unit specific implementation and these were supplemented by working instructions and relevant business processes.

- We developed a best practice guidance document for ECD aiming this to be the 'one-stop shop' for AZ-ICDE (Figure 11). This document included information on training, access to production system, folder structures and naming conventions, how to set up project/study, validation, data transfer, vendor appendices, and how-to guidance for the "ECD ways of working" in AZ-ICDE.

- We also communicated ECD AZ-ICDE guidance and processes via newsletters, emails, training and team meetings throughout the implementation period. The users also played an important role by embracing the new system as explained in the previous sections.

Figure 11: AZ-ICDE SOPs and ECB processes & guidance.



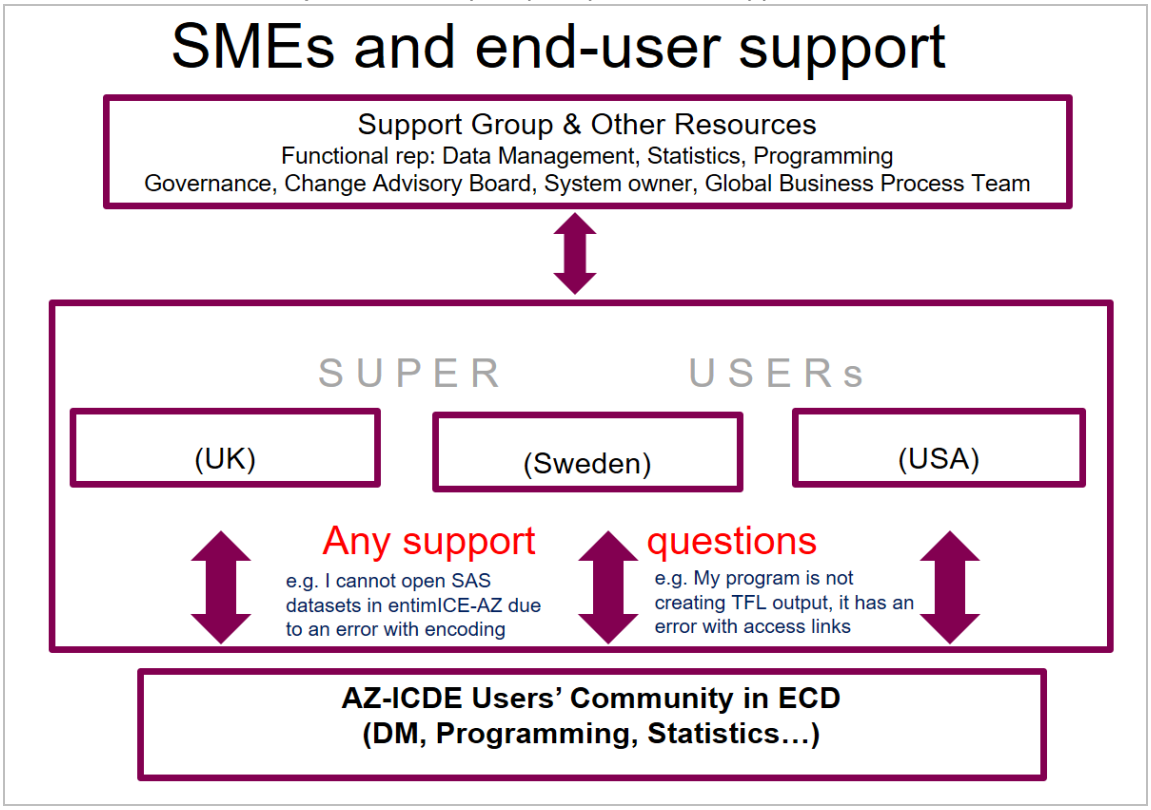
BUSINESS AS USUAL

Handing over a new service or tool from one department to another, even within the same organisation, is often more difficult than it sounds. In addition, handing over to another team that lacks the history, understanding and activities of the project makes the task even more complicated. To transition AZ-ICDE successfully from the deployment team to the ECD Business As Usual (BAU) team, we put together a clear transition plan (Figure 12). It was important to hand over enough information to the BAU team so that they would be able to provide end-user support, and interact with the AstraZeneca AZ-ICDE global support organisation (e.g., superusers or Subject Matter Experts [SMEs]).

In order to have a group that would support the end-users across all locations of the ECD organisation (e.g., Sweden, UK, USA), an ECD SME group was formed which replaced the hypercare. SMEs were selected from biometrics programming and at each site. The rollout of the SME team was communicated to end-users via emails, newsletters and team meeting presentations. The SME transition was rolled out in a phased manner where the BAU team was invited to the deployment/hypercare team meetings to enhance their knowledge about the project. They were also offered additional support and training as necessary by the hypercare team. The expectation of the SME role was discussed and agreed with both SMEs and their line managers. Below are some example tasks that were covered by the SME team.

- Collaborate with the AZ global SME network.
- Plan and allocate time to enhance knowledge about the system and its functionalities.
- Take ownership of guidance and best practice documentation,
- Prioritise and provide end-user support.
- Gain good understanding of relevant business processes.
- Seek for solutions how SAS GRID and AZ-ICDE can be used together.
- Agree on tools for end-user communication.

Figure 12: BAU transition and Subject Matter Expert (SME)/end-user support model.



BENEFITS/LEARNINGS:

- During the phased SME transition period, they were tasked with providing end-user support, contributing to guidance documents, supporting onboarding for new starters, and providing updates in team meetings. This worked well as on-the-job training for SMEs while operating the business as usual.
- Resource allocation moving from hypercare to BAU was difficult to estimate since drug project work tends to be prioritised over general support activities, but need was also driven by the system stability.
- ECD was also introducing a new delivery model which increased the number of end-users requiring onboarding training.
- The SME role and scope were not described enough which caused some unclarities between hyper care and BAU teams. This could have been avoided by detailing the responsibilities and resource allocations from the very beginning.

THE NEXT STEPS

The AstraZeneca strategic vision to have a "single source of truth" regarding clinical study data is being realised by ECD biometrics alongside the other science units at AstraZeneca. The legacy A&R systems have been decommissioned and we have started to bring in other functions in ECD into using the new system, to allow them to perform reviews, quality control and quality assurance tasks on the clinical data. New awareness sessions for the study teams, consisting of physicians, project leads, and study management have been performed for ECD, expanding the usage of the platform. The system is also helping us to promote a single platform to store non-standard clinical study data e.g., methodological, externally-sponsored studies. AZ-ICDE provides functionalities to support external collaborators and vendors to work within the system. This is an area where we hope to work with the other science units to bring more efficiencies in the way we delivery our studies.

Re-use of clinical data for purposes other than the scope outlined in the clinical study protocol is also covered by the system. In AZ-ICDE, this has its own data re-use node where analyses of de-identified data for internal AstraZeneca purposes are stored. This area is configured with a specific hierarchy structure and access control which is different compared to the main A&R node for project and study.

We envisage that other data types, such as omics data, telemetry, images, and so forth, will become a standard practice in clinical study data collection process in the future. Although some of these data, such as genomics data, will be stored and analysed on its own optimised platform, AZ-ICDE will have an important role when analyses across platforms are performed. This perspective is covered by the strategic enterprise and transformations programme within AstraZeneca.

CONCLUSION

To implement a big and complex new A&R platform for a global organisation like AstraZeneca, our strategy needed to be well-designed, the system accurately configured, and the processes aligned to business needs for a successful launch. These deployment steps were performed in close collaboration with the iCARE team and the implementation vendors following an agreed project plan. This was a great example of collaboration between AstraZeneca science units and regarded as a successful project by the company.

Our key recommendations for deploying a new Analysis & Reporting platform based on the AstraZeneca Early Clinical Biometrics experience are:

- Early engagement by business functions in system design, configuration and change awareness.
- A deployment strategy and plan endorsed by stakeholders.
- A step-wise introduction of the new system, with inclusion of pilot projects.
- A well-considered data migration plan.
- A contingency plan for drug project deliverables.
- Active end-user engagement.
- Simplified and efficient training.
- A dedicated implementation and support team.
- Clear and detailed processes and guidance.

Most importantly it's about the journey and bringing everyone along with you, if you do it together you have a better chance of making it successful, giving it longevity and finding ways to evolve.

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