DEEP

Optimizing regulatory procedures for digital endpoints

Learnings from a proof of concept with EMA and future applicability

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Abstract

As digital measures continue to transform drug development, clinical practice, and patient experience, there is an increasing need for standardization in the development, validation, qualification, and regulatory acceptance of these measures. A multi-stakeholder project, led by the Digital Evidence Ecosystem & Protocols (DEEP), in collaboration with EFPIA (European Federation of Pharmaceutical Industries and Associations) and the EMA (European Medicines Agency) was initiated to explore whether the DEEP platform could foster and facilitate regulatory qualification of digital measures in several ways: e.g.: pre-competitive collaboration for evidence generation, structured presentation of evidence to support qualification requests and explore utility with a view to lifecycle management of qualified measures, as well as the utility of the DEEP platform to potentially facilitate aspects of the EMA Qualification of Novel Methodologies. Working with stakeholders from eight pharmaceutical companies, a real-life use case was explored to investigate the potential of the DEEP platform and Stack Model for procedural and life-cycle management. The proof of concept supported the DEEP stack model's utility to support regulatory review and acceptance of novel endpoints through standardization, data reusability, and structured approach to validation of digital endpoints.

Introduction

The use of digital measures in drug development is increasing rapidly as they provide objective, quantifiable evidence of physiological and behavioral data with the potential to offer meaningful endpoints. However, challenges remain in development, validation, and regulation of digital measures (1). There have been calls from several stakeholder groups for a predictable path for development and validation of digital endpoints, with the aim to increasing regulatory acceptance (2). The validation of digital endpoints ensures that digital measures are reliable, accurate, meaningful to patients in terms of clinical utility and satisfies relevant regulatory requirements (3, 4).

The European Medicines Agency (EMA) offers a qualification of novel methodologies (QoNM) process, as a voluntary, scientific pathway allowing developers of innovative drug development methods to qualify their instruments within a pre-defined context of use. The European Medicines Agencies Network Strategy to 2025 (EMANS) (5), EMANS 2028 (6) and the EMA Regulatory Science Strategy (RSS) to 2025 (7) have laid out strategic goals and core recommendations, many of which are facilitated by the qualification of novel methodologies platform. EMA reviewed the features of the qualification procedure and published an action plan for the futureproofing of the qualification of novel methodologies (8, 9).

To support the action plan there has been a concerted effort by industry stakeholders including the Digital Evidence Ecosystem & Protocols (DEEP) to enable end-to-end development and validation of digital measures by providing a catalog for structuring evidence and collaborative work spaces to support co-creation among key stakeholders, including pharmaceutical companies, regulators like EMA and FDA, technology providers, patients, learned societies, academics and healthcare professionals, as well as collaborations within public private partnerships (10).

As part of its product offering, DEEP utilizes the DEEP Stack Model and its checklists to bring together frameworks, advice and good practices available in the ecosystem to provide harmonization of measures across different contexts of use, as well as clarity and efficiencies to endpoint technical development and validation (2). The DEEP platform offers an opportunity for futureproofing of current validation methods through increasing transparency and re-usability of generated evidence.

To explore the potential benefits of the DEEP Platform and Stack model to foster and facilitate regulatory qualification of digital measures and life-cycle management, a proof-of-concept initiative was launched between EFPIA, DEEP, EMA representatives and eight pharmaceutical companies (the applicant team).

The objectives of the project were to support multistakeholder collaboration in the development and validation of digital measures; enable dynamic and optimized regulatory advice; structure required evidence for more relevant regulatory engagement between the applicant team and regulators via the Stack model; provide a framework for re-use of evidence for novel methodologies validation in subsequent contexts of use; enable life-cycle management of QoNM components and facilitate knowledge management (11).

This article provides a summary of the DEEP-EFPIA-EMA initiative and proof of concept, highlighting the potential of the DEEP platform and stack model as one option to structure QoNM life-cycle management. It also provides an account of learnings from the initiative and the potential to inform future development.

Materials and Methods

DEEP Stack Model and Platform

The DEEP Stack model and Platform used in the process enable the structuring of evidence for digital measures and measurement solutions.

The DEEP Stack Model consists of 3 key blocks:

- **Measurement Definition Block:** defines Meaningful Aspect of Health and Concept of Interest within a particular Context of Use.
- **Target Solution Profile (TSP) Block:** defines technology and validation standards for Digital Measurement Solutions of a particular modality to collect a specific measure.
- **Instrumentation Block:** provides the statements and evidence that a particular Digital Measurement Solution meets the requirements set forth in the TSP

For each block, layers of relevant evidence and information are defined to enable the development of well-established digital measurement solutions (Figure 1). Each layer includes more detailed checklists describing further requirements for quality and completeness of evidence. This model assists applicants in planning, generating and presenting the necessary evidence in advance, and improving the quality of regulatory submissions for the evaluation of novel measures.

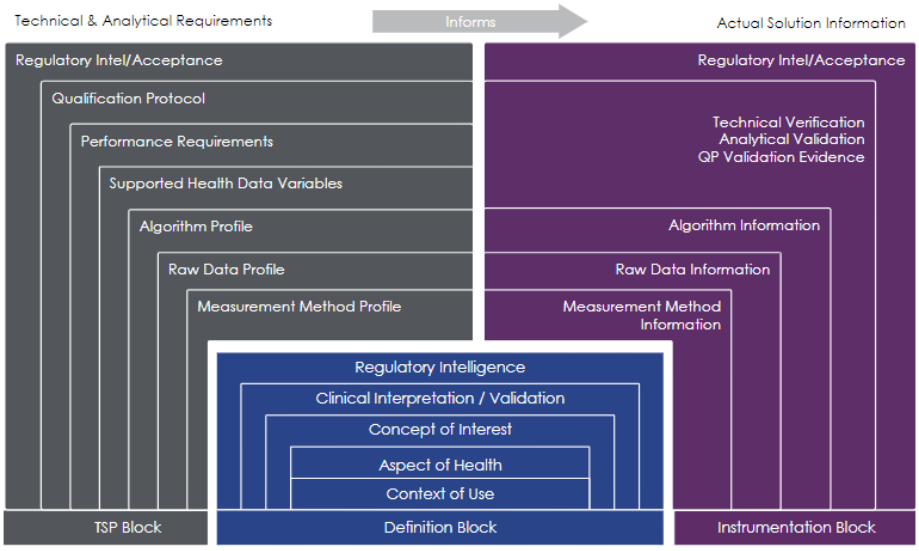

Figure 1. Layers of the stack

With the help of the case study of Nocturnal Scratch in Atopic Dermatitis, the proof of concept explored two scenarios of re-using evidence to streamline the development and qualification of digital measures and measurement solutions: 1) extending the Target Solution Profile and Digital Measurement Solution to another related disease and context of use, by re-using parts of the construct and content validity, and only providing bridging evidence as needed, and 2) leveraging an existing TSP to change components of the Instrumentation Block e.g. as technology develops, to limit the additional evidence to comparability studies or similar relevant evidence ensuring the updated component meets the requirements set forth in the TSP (Figure 2).

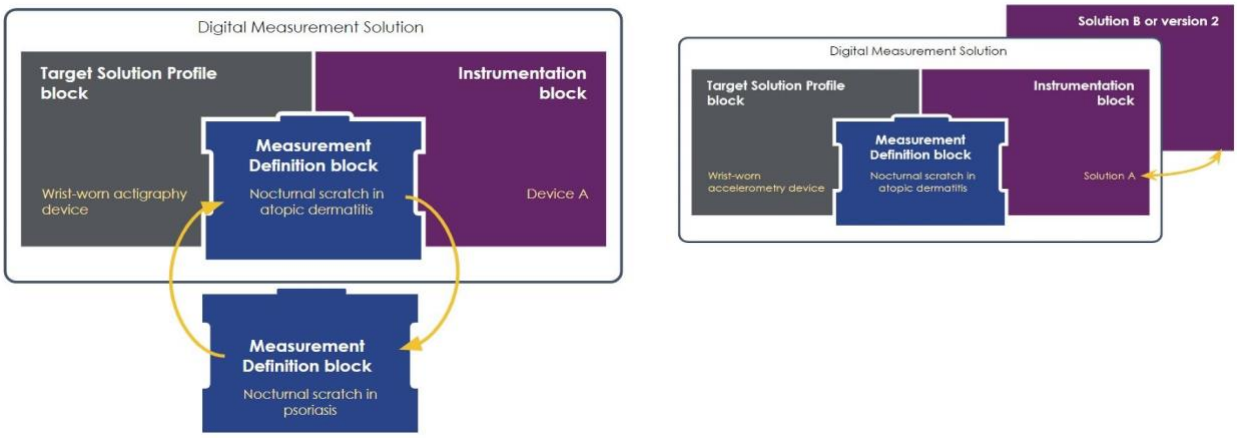

Figure 2. A) Illustration of the change within the measurement block, B) Visual representation of the discussed changes to the instrumentation block

The DEEP platform prototype used in the project provided end-user functionality that supports the workflow of the end-to-end process by enabling creation, review and submission of the procedural documentation for all stakeholders.

The applicant team structured all the information and their associated evidence through the catalog based on the DEEP Stack model, allowing creation of the definitions for the measure, technical and analytical standards in the form of a target solution profile, and linking specific digital measurement solutions to the target solution profile. The applicant team was able to present a briefing book, and supportive catalog entries, to the regulators through the DEEP platform.

Throughout the engagement with the regulators, the platform was used to review the documentation, engage in discussions through discussion boards, and to review the evidence structured according to the stack model, e.g. after the applicant had submitted the briefing book, the platform enabled its validation by the EMA. The DEEP platform enabled reviewing of each topic of the briefing book in its full context, meaning that the whole thread of question, its supporting evidence, regulator's clarifying questions to the applicant, the applicant's response, and finally the meeting notes, were all visible on a single page. This allows for storage of the regulatory intelligence acquired through the procedure for each item in the catalog, to be re-used in future development initiatives.

Proof of Concept set up

The project started in December 2022 between EFPIA, DEEP, EMA representatives, and the applicant team. In November 2023, the applicant team utilized the DEEP solution to submit their application to EMA. The system enabled a structured and evidence-based assessment, culminating in a meeting on 17 January 2024, and a debrief on 19 January 2024.

The project consisted of two stages: 1) initial scoping stage to gather feedback on the new concepts and the prototype platform, 2) conduct of an QoNM advice procedure with an applicant team using DEEP through the sandbox of an Innovation Task Force (ITF) procedure (including elements of the QoNM). Before moving to stage 2, the platform was updated to incorporate feedback received in stage 1 and the EMA conducted an IT qualification of DEEP to ensure the platform was safe and secure for European Medicines Regulatory Network (EMRN) members to use.

The following optimizations to the QoNM procedure and added benefits of using the DEEP platform were:

- EMA was able to review the briefing book and evidence in a qualification-light two stage procedure (List of Questions + ITF briefing meeting)
- The evidence was easier to navigate and enabled efficient review by the regulator team
- The feedback was organized following a structured content framework that enabled re-use
- Applicant team was able to clarify their position and provide additional input (as part of the light round of questions in preparation for the ITF meeting)
- Resulting regulatory standards (e.g. if the Concept of Interest is acceptable in the Context of Use) could be shared transparently to the public

A qualification advice-light procedure was used under the framework of an ITF meeting. Figure 3 outlines the step-by-step process for engaging with the EMA utilizing the DEEP platform.

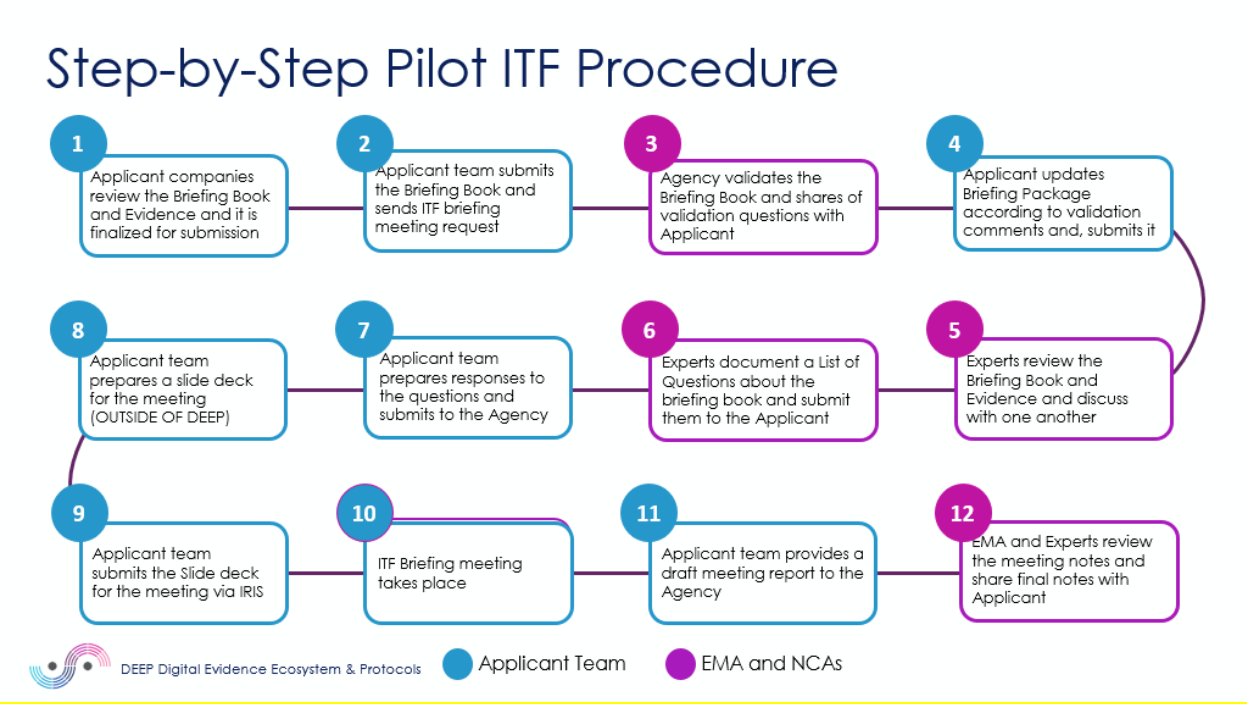

Figure 3. Stage 2 step by step journey of the procedure

Results

The key topics that were identified during debriefing sessions were: collaboration, the stack model and structure content, and future applicability. This section summarizes the findings.

Benefits identified

The applicant team found that the DEEP platform significantly improved cooperation both with the regulators and among the applicant companies. It facilitated the sharing of questions and materials ahead of meetings, providing a centralized location for all evidence and materials, which made referencing and viewing easier. This setup allowed for better engagement and interaction, highlighting the platform's potential as a regulatory collaboration tool. Although the platform wasn't extensively used during the content development stage due to limited concurrent editing features, it was noted for providing a neutral and accessible collaboration space that usually takes a long time to organize among different companies. The platform enabled working on the same version of materials and facilitated asynchronous discussions, with the stack model and catalog seen as valuable for future information sharing and innovation.

The applicant team consisting of eight different companies found the stack model to be instrumental in establishing common terminology and common approach. They appreciated the structured and readily available supporting literature and data, which brought transparency to the performance of each digital measurement solution. The Target Solution Profile (TSP) was highlighted as particularly valuable for supporting the efficient validation of new and updated digital measurement solutions by setting clear expectations and requirements. The team valued DEEP's vision of co-developing stacks in partnership with companies and regulators, which promotes innovation and development by reusing existing knowledge. They also noted the importance of endorsement by EMA and other regulators to enhance the model's credibility.

In addition, DEEP was seen as a potentially useful tool to improve the structure of information. In order to appropriately collect input from external experts, it was suggested to create firewalled group definitions in DEEP. The participants also recommended adding a customization feature to facilitate review by enabling the platform/interface to prioritize the most important and relevant information depending on each user's role and specific area of expertise.

The participants acknowledged the potential of the DEEP platform to allow for more collaborative qualification procedures both on the applicant's and qualification teams part and the value of DEEP's stack model to support the quality of scientific assessment and advice on digital measures. Furthermore, they also saw an opportunity for the platform to support public-private partnership consortia (e.g. IHI) as they proceed to qualification, ensuring their sustainability and life-cycle management, especially when there is a limited funding horizon and a sustainability plan becomes key.

Opportunities for improvement

European Medicines Regulatory Network (EMRN) experts provided detailed and constructive feedback on how to enhance the DEEP platform's functionality and usability. Recommendations included making the IT tool more interactive and intuitive for regulatory assessors, improving navigability, and enabling notifications for new comments added by the qualification team members. They expressed the need for an integrated view of all topics, rather than having comments divided by question. They also mentioned the importance of being able to provide specific comments within the document and linking comments to certain sections instead of general references. They highlighted that the independent assessment by two national reviewer teams in the qualification expert team is important and should be maintained.

For the future, the applicant team suggested several enhancements to the DEEP platform. These included the implementation of automatic save changes, document versioning, and history to improve co-development of content. They also recommended features like paraphrasing, referencing previously used resources, and structured documents to support correct document structure for different regulators. Additionally, the team expressed interest in notifications for ongoing activities, a calendar function for project timelines and deadlines, and slide creation functionality for meetings with the Agency. They also emphasized the need to address legal aspects, including IP and privacy.

Looking beyond the current use case, the applicant team expressed a keen interest in collaborating across different stakeholder groups and suggested exploring platform functionalities and services that bring together companies with similar interests. They highlighted the value of potentially sharing regulatory insights from different regulatory agencies and facilitating a consistent view across them as a key improvement. The team showed interest in using the platform for engaging with regulators and for qualification purposes. They also noted the potential for integrating digital measures, patient-reported outcomes (PROs), and patient and public involvement (PPI) as interesting extensions. Additionally, having a "Digital Health Technologies" review or literature "warehouse" with overarching guidance and go-to documents was seen as beneficial.

Discussion

The DEEP platform offers many potential benefits to support the qualification procedure, uptake, and adoption. At the time when the proof of concept ended in January 2024, the work on the platform implemented further development to incorporate feedback and learnings from different stakeholders. In the future, there is a need to further consider how assessors from national competent authorities, their internal teams, and external experts can adapt and adopt the platform in their current workflow.

Thinking beyond this proof of concept, DEEP has the potential to enable collaboration across different regulatory bodies such as the FDA, EU HTA bodies and conformity assessments by notified bodies. Further platform development should look at establishing commonalities and features supporting efficiency and improving usability across stakeholders, as well as firewalling and interoperability with the systems of all regulatory bodies mentioned. Key considerations to increase attractiveness and potential future adoption from the regulators perspective include: independence of the tool from pharmaceutical companies, inclusivity in access to the platform (e.g. involvement of academics), proactive engagement with stakeholders to meet diversity of needs, reliability of the tool/service, transparency of information, and an optimized user interface.

Regarding the acceleration of development and acceptance of digital measures, the team believed that the stack model could align all stakeholders, including regulators, pharmaceutical and technology companies, by harmonizing terms and language. The model has the potential to reduce development steps through three scenarios: extending measures to different contexts of use via the TSP, reducing development steps for new instruments with established TSPs and measurement definitions, and managing the lifecycle of solutions as technology evolves. However, the team emphasized the need for the stack to be curated and maintained to be truly impactful. They also suggested simplifying the stack model by avoiding acronyms and optimizing its presentation.

The applicant team identified several key considerations for enabling the use and adoption of the DEEP platform. They emphasized the need for more content on the platform, such as currently available measures, and the ability to share this content outside of partnerships. They also suggested curating more showcase stacks that demonstrate concrete examples, like the stack built during the project, to illustrate the stack model's value. Starting new projects to create success stories and maintaining momentum was seen as crucial. Additionally, they recommended creating new use-case scenarios to highlight different ways of utilizing the platform and bringing the ecosystem together by aligning different regulatory bodies like the FDA and EMA, as well as engaging members from all stakeholder groups, including tech companies and patient associations.

Looking ahead, future improvement can be achieved across several areas such as the stack model, life-cycle management and supporting the harmonization of regulatory requirements. This project highlighted the potential of the stack model to: facilitate harmonization across applicants by focusing on important key validation principles such as Context of Use and Concept of Interest; utilizing the logical structure of the stack model, which divides critical validation steps/information into relevant sections or components. The potential for reusing components of the stack model to extrapolate/extend to alternative Contexts of Use and support lifecycle management was seen as particularly attractive and beneficial, although it could not be fully explored with the selected use case for the proof of concept.

In terms of life-cycle management, extension to new Contexts of Use is another area for future development. In terms of reusability, the same Meaningful Aspects of Health and Concepts of Interest may be relevant to patients with different diseases. Therefore, the same instrumentation block and target solution profile may be used to collect the measure in those new disease areas. This strategy aligns with previous studies that utilize prior research. Bertha et al 2022, described a framework for leveraging prior work to demonstrate a digital health technology and digitally derived endpoint is fit-for-purpose (12).

The proof of concept was considered informative by all participants. However, not all concepts could be tested as there were limitations due to the case study selected for the procedure and the limitations of the platform. The EMA encouraged the EFPIA-DEEP team to identify an applicant team that could go through an entire QoNM (potentially across different Contexts of Use) so that the full value of the DEEP system can be used.

Next steps in the nocturnal scratch development program include design and planning of a clinical validation study. Seeking regulatory feedback into the design is envisioned and the DEEP platform could provide a suitable mechanism for this and another QoNM engagement for this purpose can be considered, and this would allow the centralization of input received from other agencies as well.

DEEP is committed to providing access to identified regulatory standards publicly, in line with current trends of transparency. For the proof of concept, DEEP has curated the key regulatory feedback received by the applicant team on the platform. Based on the feedback collected in the project, the DEEP platform will be updated with the key identified features. Furthermore, content will be curated on the platform with different digital measurement components. The platform has been launched in an early access program and DEEP is working on expanding this launch to more stakeholders, including academia and patients as well as to create advisory boards with external stakeholders to understand their needs, collect their feedback and connect to key experts.

The DEEP-EFPIA-EMA proof of concept suggested the DEEP stack model's usefulness in endpoint qualification by providing a platform for structure and standardization of digital measures, supporting lifecycle management through reuse It may also serve as a collaboration platform for regulators, health authorities and notified bodies provided interoperability, IT security and data protection aspects meeting regional legislation can be implemented as appropriate and move towards a connected ecosystem for the qualification and use of novel digital endpoints.

Author Contributions

All authors meet the four criteria detailed in Author Instructions. The authors LL and MM were responsible for concept and design, creation of figures, drafting and revision of the paper, final approval, and accountability for the work. CdG, BG, RTW, PY, AC, IK, FIS, KL, CL and CN were responsible for elements of design, drafting and revision of the paper, final approval, and accountability for the work

Competing Interests

The authors declare no competing interests.

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