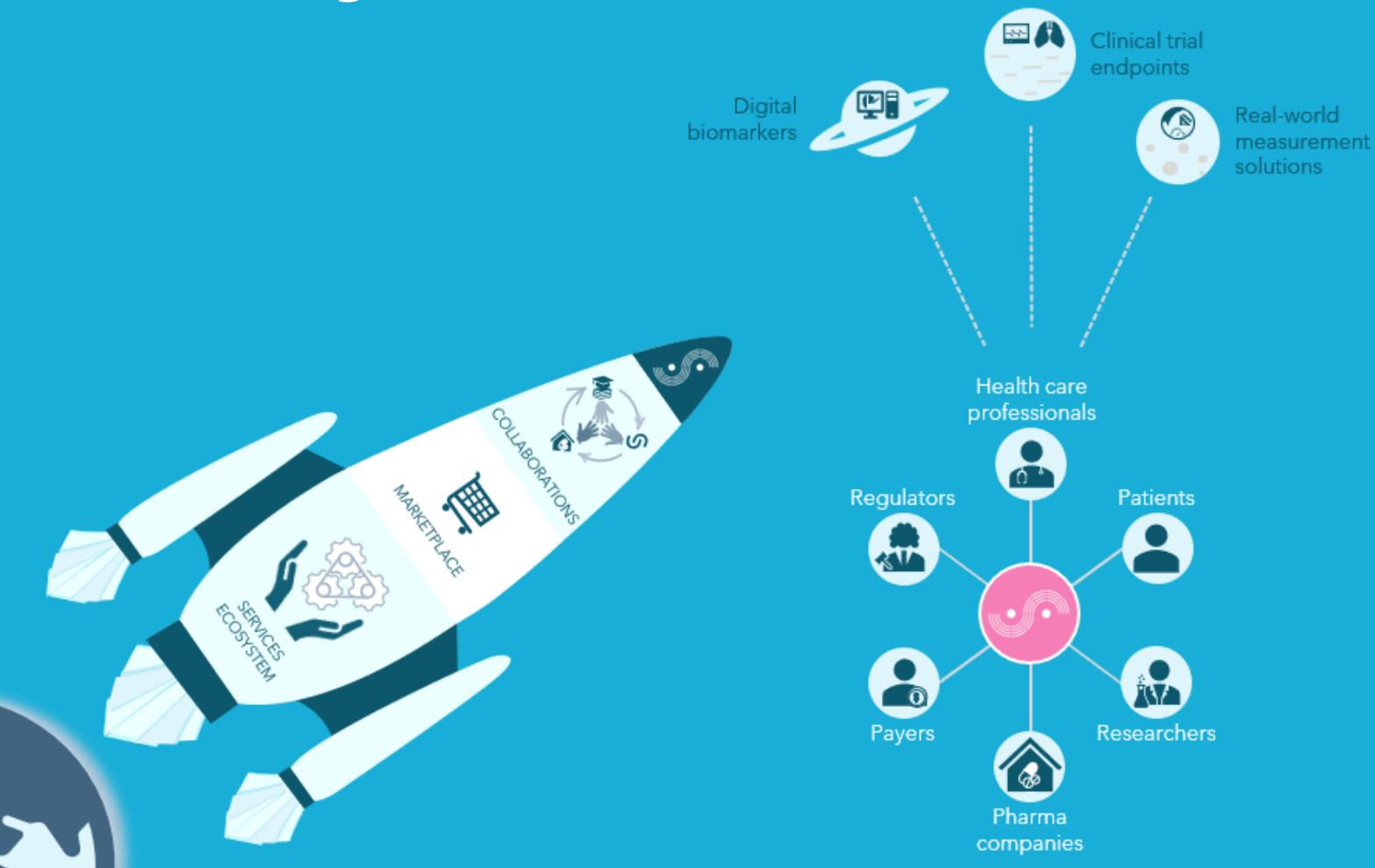
DEEP™

DIGITAL ENDPOINTS ECOSYSTEM & PROTOCOLS

An accelerator for the digital measurement ecosystem



ABSTRACT

Digital measurement solutions can be found in various forms (e.g. sensors, wearables) and have a wide range of applications; as such, they can be very useful in the life sciences sector. However, implementing their use in evidence generation can be complex, which prevents the stakeholders from fully taking advantage of these solutions. Our initiative, named Digital Endpoints Ecosystem & Protocols or DEEP, aims to resolve this issue. DEEP is an accelerator for the digital measurement ecosystem, offering a marketplace and service protocols that accelerate the adoption of digital measures. DEEP is about alignment, collaboration and asset re-usability across the life sciences domain. The DEEP Marketplace covers assets for digital biomarkers, clinical trial endpoints and real-world measurement solutions. It facilitates asset trading and provides a unique offering of services for the discovery, development and further adoption of reliable digital measurement solutions in healthcare and the life sciences industry. The DEEP Service Protocols define a set of novel services for the holistic development and management of digital measurement solutions. DEEP will bring together the innovative ideas and expertise of academics, clinical researchers, technology companies and service providers in order to deliver custom digital measurement solutions which are optimized for performance and validated for their intended use cases. We believe that the adoption of digital measurement solutions will lead to improved capabilities to measure aspects of health most meaningful to patients and enable evidence-based, patient-centric smart medical intervention services. The DEEP initiative will therefore play an important role in digitizing the pathway to develop and deliver patient care, where clinical decisions can be based on patient-centric insights generated by fit-for-purpose solutions.

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INTRODUCTION

In the past decades, patient reported outcomes (PRO) have been successfully used in clinical trials. They are great tools to understand how patients cope with their disease and represent an added value to traditional clinical endpoints. Digital measurement tools have a wide range of applications and can be very useful in the life sciences sector; however, implementing their use in clinical research is not without complications. As a result, the pharmaceutical industry does not yet take the full advantage of what digital measurement tools can provide. Our project, named Digital Endpoints Ecosystem & Protocols or DEEP, aims to resolve this issue.

1. What is DEEP?

DEEP is an accelerator for the digital measurement ecosystem.

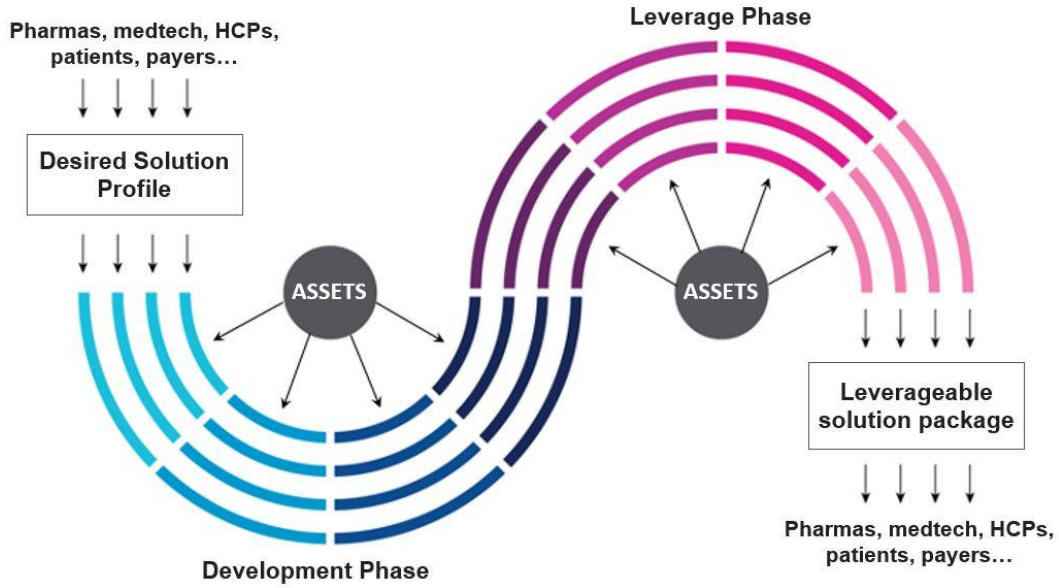
A robust framework already exists for the development and use of PROs in research and care settings. The digitalization of these PROs is commonplace, but the digitalization challenges have not been comprehensively addressed over the years, which has hindered the adoption and created inefficiencies and inconsistencies, despite broad use within the industry since the late 2000s. DEEP offers to improve the inefficient trial-and-error process associated with the adoption of new technologies and approaches by offering a practical services framework and marketplace. With DEEP, we can accelerate the maturity of the entire digital measurement ecosystem.

To achieve this goal, DEEP offers a marketplace and service protocols.

The DEEP Marketplace facilitates trading in measurement assets and provides a unique offering of services for the development and sourcing of digital measurement solutions for various use cases in healthcare and the life sciences industry. The Marketplace covers assets related to Digital Biomarkers, Clinical Trial Endpoints and Real-World Measurement Solutions.

The DEEP Service Protocols define a set of novel services for the holistic development and management of digital measurement solutions. DEEP provides the structural design framework for the services, ensuring their consistency and compatibility within the ecosystem. Some services are offered by qualified organizations, vetted within the service ecosystem, and others by the DEEP framework.

One of DEEP's main purpose is to bring alignment, collaboration and asset re-usability across life sciences.



The DEEP logo depicts the harmonious nature of these services – services often depend on each other and the framework offers an efficient transition between phases and organizations.

DEEP aims to improve collaboration between different parties including those outside of the traditional stakeholders within the pharmaceutical industry. DEEP offers a platform where it is possible to:

- leverage the work done by other parties;
- make assets available to other parties;
- ensure that the industry becomes, and stays aligned on what the digital measurements should be, i.e. that the definitions and interpretations of these measurements do not vary over time or across organizations.

2. Where did the idea behind DEEP originate?

DEEP originated from observing the increased interest shown by researchers and scientists to use digital measurement solutions in clinical research and the complexities they encountered. Because implementing these solutions is a novel and complex process, we sought to develop a framework to guide these researchers. We leveraged the foundation established by various digital health pioneers (such as the Digital Medicine Society (DiME), the Clinical Trials Transformation Initiative (CTTI) and the guidance issued by regulators such as the Food and Drug Administration and European Medicine Agency) and built from it to create DEEP. DEEP started as an internal project, but it soon became clear that the framework would also benefit others and that other experts in the industry were willing to support creating it. This is how DEEP was transformed into a cross-industry initiative. Going beyond pharmaceutical companies, it also became clear that various stakeholders needed to take part in this initiative for it to be successful, including regulatory bodies, technology companies, service providers and academic researchers. These different parties have important roles to play for DEEP to reach its full potential.

3. What is the process to go from a research question to a digitally measured endpoint validated for patient use?

Similar to drug development, there are different phases involved to bring the idea of a digital measurement solution to real-world use. Each phase plays a crucial role to ultimately get the acceptance required by the different stakeholders for the use of these solutions. The key steps – each supported by a corresponding DEEP service – are detailed below.

- **Asset Search:** This service is about how research teams discover the availability of existing solutions and components to accelerate their work and avoid duplicative efforts. The search can return

either ready-to-use solutions, less mature ones, components or nothing at all. From the search, researchers get valuable information for decisions about research plans and study designs, and on how they can proceed with the procurement of leverageable assets. The service provides additional value with advice on how to position available assets within a specific research context.

- **Measurement Definition:** Definition of WHAT is meaningful to the patient experiencing a certain condition. It defines what is essential to know for detecting meaningful changes in the health of patients suffering from a disease. This definition is supported by evidence, either through literature search, qualitative research methods or by other means. Once a working definition is created, it is published along with supporting evidence and requested for comments by health authorities and other relevant stakeholders. The final version is listed after refining the last version based on the comments. This version then establishes a standard that others can follow to ensure alignment within the same condition and measurement definition.
- **Asset Leverage:** Once customers have figured out which assets they want to leverage in their research explorations and why, they need to acquire the right permissions before they can actually use them. Asset Leverage service simplifies this journey right from choosing the assets to finally acquiring the rights for use. They strategically manage to leverage the right asset for the right job at the right price, on behalf of their client, using standardized access mechanisms. Once all that is done, this service also delves into the complexities of relevant laws to draft the contracts to legitimize the agreement between all parties involved.
- **Prototyping:** If the Measurement Definition service defines the WHAT of an endpoint, the Prototyping concept service provides the HOW and produces a feasible technical prototype of a measurement solution to measure what the definition calls for. This is a highly technical service, often combining data and machine learning expertise with evaluation of sensor technologies. Prototypes are often produced through a process of trial-and-error, also tapping into already existing components of data, algorithms and sensor technologies that exist in various databases and marketplaces. The end result is a prototype measurement solution that can feasibly capture the Measurement Definition.
- **Analytical Validation:** Once ready, the prototype enters the Analytical Validation stage. This step ensures that the digital solution adequately performs as intended. Once completed, evidence supporting the technical performance of the solution are available.
- **Clinical Validation:** The Clinical Validation stage generates the evidence necessary to support the clinical interpretation of the measure and is suitable for operational, regulatory and clinical decision making.
- **Dossier Development:** The DEEP ecosystem supports and enables the distributed development of digital measures as well as the use of those measures in research explorations, accelerating the process. Dossier Development is the service that supports

the customers with developing their dossiers by evaluating all the evidence generated throughout the research's lifecycle but aggregating only high-quality evidence. Finally, the aggregated evidence is processed to put together a dossier, ready for submission.

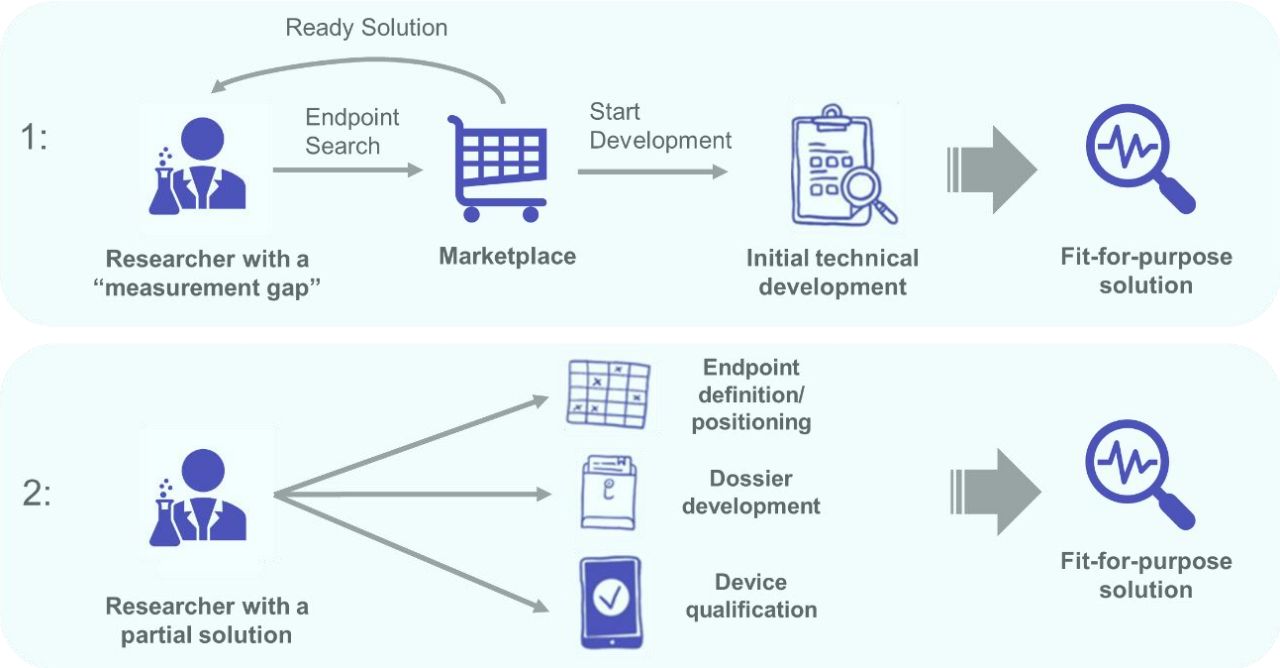
- **Profiling:** Once a solution for capturing a Measurement Definition exists, it can be abstracted into a Target Solution Profile (TSP). The TSP identifies the key components of the measurement solution for a specific definition. The components may include hardware, software and firmware, usage instructions and any other aspects of the measurement solution that is critical to its functioning. The TSP are generic and, instead of referring to any specific brand or model, the specific components of a measurement solution are abstracted into generic descriptions. This enables different measurement solutions to be created. For example, using different hardware components that all implement the same TSP and thus can be used as a measurement solution for the same definition. Each Measurement Definition can have multiple TSP and each TSP can have multiple solutions. The TSP increases the diversity of measurement solutions available and enables the upgrading and subsequent validation of measurement solution component upgrades through the use of QP.
- **Validating Qualification Protocols (QP):** Unlike many other types of measures, digital measures have a rapidly evolving lifecycle where components of measurement solutions (sensor technologies, algorithms, etc.) need to be upgraded frequently. It is not practical to re-execute all of the original validation work every time a component is upgraded. Instead, simpler QP can be executed. QP can be developed for a measurement class and can be very streamlined compared to the original validation process. Some QP can even be fully automated, for example, an algorithm upgrade can be automatically validated against a reference dataset. However, QP must be validated through a reliable, evidence-based validation process.

4. Is it possible to use DEEP at different stages of the digital measurement solution development?

Absolutely. It is possible to use DEEP at the very beginning of the process for researchers with a "measurement gap". DEEP can offer end-to-end support with different services and the marketplace until the digital measurement is ready for use.

Another typical starting point is to use DEEP to complete missing elements of an existing solution (for researchers with a partial solution). These partially ready solutions can be completed with compatible assets from the marketplace and/or by tapping into the DEEP services.

DEEP can enable researchers at almost any stage, via the use of the marketplace, the services or by enabling collaboration between parties with the same interests.



The assessments which are traditionally used in clinical studies and care settings are scientifically validated and stable through years.

5. How do you ensure that the digital solutions created through DEEP perform well and are supported by evidence and remain so, despite ever evolving technologies?

As you can imagine, generating all the evidence to ensure that a measurement solution is fit-for-purpose is a lot of work, even with the DEEP services. It would be very inefficient to have to repeat all this every time a solution or a component changes. It will be very impractical too, because these solutions often have multiple components that can each have their own rapid lifecycle. This is a challenge in the context of a clinical development program, which might take ten years to complete and will need to be able to collect a consistent body of evidence throughout the program. The same challenge is then multiplied between companies, because regulators and other

stakeholders need to be able to compare products. That becomes very hard if everything is measured using different techniques without evidence supporting the equivalency of such measures. To deal with this complexity, DEEP offers a framework that can establish standards for measurement classis and a mechanism for establishing evidence-based equivalency between solutions and versions within the same class. This way, results from studies can become much more comparable without the huge burden of having to repeat all of the validation work every time.

6. What is the DEEP Measurement Solution model?

The DEEP model can be divided into 4 parts as follows:

Part 1: Measurement solution components can be defined as: (i) the Tool can be a sensor (a device that generates raw measurement data) or a software & hardware combination of solutions deployed to capture the measurements of interest, (ii) the Data refers to the information captured by the sensor, (iii) the Algorithm refers to components present at any level of the measurement solution involved in the processing of the sensor generated data, in order to produce a meaningful metric (e.g. conversion of raw data into a step count), (iv) the Analysis will allow the conversion of the sensor generated data to an understandable insight (e.g. the length of continuous walking bouts).

Part 2: For a chosen digital endpoint measurement solution, there are 3 core aspects which, brought together, form the basis of the Measurement Definition: (i) the Condition refers to a combination of the condition that is being investigated and of the population enrolled in the trial, (ii) the Effect refers to the expected outcome after a medical intervention, (iii) the Measurement (concept of interest) refers to the quantitative measure correlating to a meaningful aspect of health that has been chosen to demonstrate the benefit or effect of an intervention.

Part 3: The next piece of the stack is the evidence to support Clinical Interpretation, which allows us to understand the measure in its clinical context (e.g. to understand the minimum rate of change that is clinically meaningful). As a result, this evidence enables clinical and regulatory decision making and could be referred to as "Clinical Validity".

Part 4: These items and assets need to be brought together to for Digital Measurement Solutions. DEEP defines the role of the Custodian, who is a party that is responsible for assembling the final solution into a package, along with the evidence dossier that documents the evidence supporting the use of the measurement. The Custodian packages these assets into an offering that can then be made available to end users through a well thought out access mechanism that meets the needs of end users as well as the interests of the asset owners. The Custodian could be thought of as the copyright holder of a digital

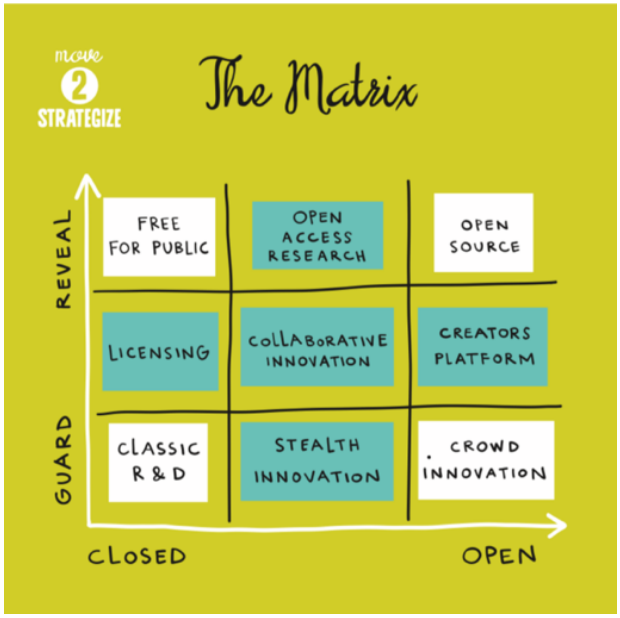
measurement solution, they operate the DEEP leverage package.

The different assets included in the Marketplace are available to different parties to be used as complete solutions, or as individual component parts that can be assembled to form new solutions. DEEP diverges from traditional unidirectional buyer-and-supplier based marketplaces due to its collaborative nature, and parties would often find themselves operating both on the provider side as well as a customer. Customers can acquire assets that already exist in the marketplace, but they can also announce their interests and intent to create something new, allowing others with the same interests to join in or offer parts of the solution. The marketplace can multiply the value of individual assets, enabling a single component to be combined to be part of multiple complete solutions, therefore making it easier for customers to find and leverage fit-for-purpose solutions, or key parts for new solutions.

To ensure the digital measurement solution ecosystem fulfills the promise it offers, it is crucial that many parties collaborate and agree on the same definitions and interpretations. The more accepted and standardized a definition is, the more weight it will carry.

7. How do you envision the DEEP Marketplace?

It is our aim to make the DEEP Marketplace a collaborative experience. Nowadays, many companies are hesitant when sharing innovative ideas or assets. This is partly because people and companies do not always have intellectual property (IP) strategies in place or the mechanisms to effectively execute them.



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The IP Innovation Matrix is a good way to illustrate the different possibilities to deal with IP. In a classical research and development setting, new discoveries are closely guarded. The DEEP Marketplace aims to enable multiple options with different degrees of openness and collaboration.

DEEP aims to remedy this, by offering a well-defined menu of options with standardized legal templates to organizations wishing to make assets they own available to others through a mechanism of their choice.

8. Practically, how do I acquire an asset?

If you are a service provider

You can extend your current service offerings with the ones described in the DEEP Service Protocols. Once vetted as a DEEP service provider, you are an integral part of the ecosystem, and we can match your services with customers that need them.

If you are a technology company

You can approach the DEEP Marketplace and request your asset to be listed. As the asset owner, you can define how you would like to make your asset available to others (e.g., open-source, free for public, or licensed). DEEP offers Asset Listing Services to evaluate your asset and find the relevant connections for it. This allows measurement developers to find your asset easily and incorporate it into complete, fit-for-purpose solutions. You may find that your asset will be re-used and repurposed to be part of many solutions, increasing the value of your asset.

If you are a clinical researcher

You can use the DEEP Marketplace to find a solution for your research. You could find a full endpoint stack that you will be able to purchase and use as is in your research. You may also find a partial solution and then use the other services that DEEP offers to find the missing components to create a solution that will serve your needs.

9. With DEEP in place, what will the future look like for patients?

We live in an increasingly intelligent world filled with smart phones, smart cities and cars that operate with a degree of autonomy. Digital technologies are widely used for personal health management, with activity trackers, smart rings and other clever solutions. In terms of smart medicine, we have barely scratched the tip of the iceberg, leaving tremendous potential untapped for creating new medical interventions. In addition, new intelligent capabilities could identify the right individuals for the right treatment and allow remote monitoring by experts or even self-measurement by patients. Realizing the vision for DEEP will improve the capability for the ecosystem to develop new measurement solutions. These solutions would allow to select those aspects of health most meaningful to patients and to target them with their interventions. Combining medical interventions and services with the measurement capabilities is

what is required to drive the life sciences industry towards meaningful digitalization and reach the same level of intelligence that we see already today in most aspects of our society.

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