Digital Devices in Clinical Trials

Most pharmaceutical companies are investigating how digital devices can be utilised in clinical trials to improve the data foundation and potentially assist in securing a faster time to market and improving patient retention. One common challenge stands out: how do you create a setup robust enough to allow you to include the output data as evidence? This article discusses the common challenges faced and, based on network consultations with a group of pharmaceutical companies, it seeks to identify a viable path forward.

The use of devices in clinical trials has been standard procedure for many years: syringes, spoons and other analogue devices are used but technology is evolving rapidly and at a pace where it can be difficult for regulated industries like life sciences to keep up. With the introduction of digital devices, it has become almost impossible for pharmaceutical companies to keep up with the development.

The reality is that you can pick up consumer digital devices in local electronics stores, monitoring the human body, generating high-quality, reliable, real-time data in a non-intrusive way. These devices are more advanced than any device a pharmaceutical company would be able to produce, as this requires state-of-the-art technology competencies and expertise.

These devices are capable of monitoring such things as: heart rate, activity weight, composition of food intake, blood sugar, acceleration, skin condition, moisture, sleep and much more. The devices range from more classic wristbands, to socks, wall-mounted sensors, ingestibles and bio tattoos. Each device fits a purpose and a situation, and with the accelerating pace of innovation, it is not difficult to find a capable device.

Challenges in Clinical Trials
In clinical trials today, some of the biggest challenges are:

- Patient retention: The attrition is high in most trials and part of the reason is the patient’s time spent in doing measurements, showing up for interviews, etc.
- Time to market increases: more and more evidence is required and requirements are constantly increasing.
- Drug candidate selection is becoming more and more difficult: with more and more drugs on the market, the identification of candidates takes more time and better data is needed to be able to more quickly deselect candidates and focus on the right candidates.

How do Digital Devices Improve the Outcome of a Clinical Trial?
The big question is why all of these technologically advanced devices, and the valuable data they generate, are not fully utilised to secure a faster time to market, improve the data foundation to select the right drug candidate and secure an easier collaboration with the patient?

Through a series of meetings and network consultations with the industry, NNIT has sought to identify the biggest challenges and obstacles to successfully utilise digital devices in clinical trials. The companies participating range from mid-size pharma to top-10 pharma companies, covering various therapeutic areas from diabetes and neuro-degenerative disorders to depressive disorders and dermatology. Part of the group had tried to use digital devices in clinical trials, but not succeeded in implementing a sustainable setup that could ensure that data could be used as evidence in the clinical trials.

The main challenges outlined and identified at these pharma companies were:

1. Device selection
2. Device validation
3. Device management
4. Data transfer
5. Data consolidation
6. Unclear guidance from authorities

Device Selection
Many pharmaceutical companies find it difficult to cope with the rapid development of the market, making it difficult to get an overview of the devices on the market and how they can support clinical trials. Furthermore, the project managers running the clinical trials rarely have much technological experience, making it difficult to grasp the opportunities that the device in itself can present. An imminent need is seen for support in presenting relevant digital devices based on input on the clinical trial itself; making sure to present only devices of relevance, and potentially a mix of devices, to support different angles of the clinical trial.

Device Validation
In order to use the data output of the device as evidence in your clinical trial, it is a prerequisite that the device is approved through a proper device validation. While many companies are experienced with validating devices, very few know how to get a digital device approved.

FDA has set up guidelines to follow on how to validate the devices. Once approved, they are open to use for everyone and it becomes available on the approved device list. That means that there will be a hill to climb and the first companies must expect to put some resources into validation of devices. But over time, the list of approved devices will increase and it will be more and more obvious to choose from this list. Currently, however, this list is too short.
Device Management
A low-practical, but challenging part of using devices in clinical trials is being in control of which patient has which device, monitoring the status of the device itself, delivering training and software updates, versioning and the low-practical part of handing out and returning the devices.

Device management may be a new discipline in the clinical trials arena, but is something which has been solved many years ago in other lines of business. Just think about how how your current employer manages devices as cell phones. Similar methodologies and approaches can be used for clinical trials, leveraging the experiences and expertise already existing.

Secure Transfer of Data
As most devices are coming from different vendors, the available data platforms are diverse. It basically means that with each device, you get a new, typically SaaS, solution, from which you need to fetch the data. This is smart for consumers, but poses a big problem for a pharmaceutical company wanting to use the data in a clinical trial: 1) It is difficult to guarantee the data transfer end-to-end ensuring data integrity, that is, that no changes or interferences happen; 2) the cloud platforms are open, non-validated, rapidly updated platforms, which makes it difficult to stay in control of what happens to the data after the transfer; 3) each device has its own data format and output, typically incompatible with the others.

In regard to transfer of data and consolidation of this, a digital device is, however, not much different from any other application; the software is as advanced and comes with several features. Again, methodologies and approaches used elsewhere in IT can be reapplied. Experience and tools used for doing integrations and interfaces from the device itself and to a specific target can be set up, potentially feeding data into a data hub that consolidates and prepares the data to be ingested into the clinical applications of your choice.

Storage and Consolidation of Data
After the transfer, the pharmaceutical companies need a consolidated dataset from all of the devices. This to avoid doing endless interfaces to your clinical systems, as setting up and maintaining such interfaces does not serve as an option as these are costly, and are often updated and changed. Instead, an intermediate layer is needed. Here useful data management tools can be used to combine, standardise and prepare the data to be moved to the clinical systems of choice. In this way, you create a buffer between the rapidly changing world of new devices and the stable and validated world of clinical systems. This allows for flexibility and scalability, enabling you to continuously add and introduce new devices into your portfolio of clinical trials.

Unclear Guidance from Authorities
Even if there is a solution to the above five key issues outlined by our network group, some inaccuracies and lack of clarity in guidelines and regulations from authorities have hindered some of the speed of the technology uptake. FDA has addressed this head on, and announced publicly at the DIA RSIDM conference in North Bethesda, MD in February 2018, that “FDA wants to change the perception that such regulations as CFR 21 Pt. 11 hinders the technology adoption in pharma and while staying in control, (they) want to modernize the requirements to fit the modern world”.

Concretely, this means that CFR 21 Pt. 11 has been updated and some guidance given to address a range of concerns. FDA mentioned five areas of concern that they had addressed. It is important to state that below is a summary of an open session held at the conference; the exact details and explanations will be found when the updated version of CFR 21 Part 11 is published.

Access Controls
A lot of discussion has been ongoing on what requirements to access controls exist with regard to digital devices. Some devices do not come with screens or means of input, such as an ingestible, and some, for example a smartwatch, have a screen, but it would be almost impossible to implement access controls.

The guidance that FDA gave was to:

- Ensure access controls are in place for mobile technologies that rely on user entry.
- Obtain signed declaration from study participants, confirming that the device is solely used by the study patient.
- The above only applies if the device is not an ingestible.
- This answers these discussions and makes it much clearer what is actually needed.

Location of Source Data
The location of the source data has been a hot topic. If it is considered on the device itself, suddenly GxP validation could apply for a wearable, which is difficult to apply.

FDA came with some interesting statements:

- FDA does not consider the mobile technology to contain the source data.
- The earliest retainable record of the data is seen as the first destination after the mobile device.
- FDA will not inspect individual mobile devices.
- FDA will focus on the process for capturing, transmitting and recording the data from the device.

This is a small breakthrough on how you need to work with mobile devices in clinical trials, and it shows that the variety of devices you can use will be bigger, as long as you are in control of the data flow from the device and to your clinical systems, where CFR 21 part 11 applies.

Audit Trails
The digital device must record date and time stamps and transmit data, but only the first destination should capture a full audit trail including originator of the data. Once data has reached the first destination, only clinical investigators, delegated study personnel or similar personal should be authorised to make changes. All changes must be tracked by audit trail. This again opens up the use of standard devices while the strict requirements apply to the software systems that capture the data.
Security Safeguards
Some of the safeguards, which were discussed and given as best practice, were:

- Digital devices must ensure security and confidentiality of data.
- Data must be encrypted.
- Depending on the technology, appropriate measures such as remote wiping, remote disabling, firewalls, etc., must be considered.

In other words, the sensible safeguards that you can take are the ones that you must implement.

Training
It is stressed that appropriate training must be conducted of patients to ensure correct output data and to avoid misuse and wrong use of the device, which could potentially alter the data. The interesting thing is that it was made very clear that training must occur before hand-out of the devices as well as during the trial, in order to maintain a proper level of knowledge and avoid bad habits.

So How Do You Proceed From Here?
It may still seem like a lot to accomplish to use a digital device in a clinical trial; however, the output of doing so can have a significant impact on patient retention, assisting in faster drug candidate selection and overall time to market. It is important to realise that digitalisation has now entered the scene of clinical trials. It is no longer a question of whether you should do it, but rather how. It is evident that new types of skills and profiles are needed, some with more IT experience and merits in that space. But it is also an area that evolves so rapidly that it does not make sense to try to keep up with the developments entirely on your own. You need to build strong relationships with a partner that can guide and set direction together with you. Furthermore, it is crucial to follow the different programmes and guidelines that authorities launch to fast-track some of the innovation.

You may see competitive advantages arise from participating in exactly such programmes as the FDA digital health software recertification programme and read the FDA Digital Health Innovation Action Plan to see how authorities see the new world of digital innovation.

REFERENCES
2. FDA Digital Health Software Precertification (Pre-Cert) Program: https://www.fda.gov/MedicalDevices/DigitalHealth/DigitalHealthPreCertProgram/default.htm

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