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D-FLEX® ECOSYSTEM – FROM DATA TO VALUE

Here, Fred Metzmann, PhD, Vice-President Sales and Marketing, and Frank Leipold, Business Developer Digital Solutions, at Haselmeier, discuss the benefits of connected medical devices in clinical trials and describe the advantages of Haselmeier's D-Flex® Ecosystem for improving adherence and reducing the dropout rate in clinical trials.

In recent years, interest in, and adoption of, connected technologies has grown significantly within the drug development industry, due to their potential for improving healthcare delivery, research and the patient experience. The use of connected digital products, such as those that capture physiological and behavioural metrics, in formal clinical research has also been steadily gaining in prevalence and importance for several years.[1]

Currently, many pharmaceutical companies are exploring how connected digital devices can be incorporated into their clinical trials to improve the data foundation and, potentially, to assist in securing a faster time to market and improve patient retention. However, one of the biggest challenges that remains to doing so is the creation of a work structure that is robust enough to allow the output data from connected devices to be accepted as evidence for the trail.

To this end, Haselmeier has developed the D-Flex® Ecosystem, a flexible digital solution that works with Haselmeier's D-Flex® disposable injection pen. The D-Flex® Ecosystem presents significant advantages for improving the robustness and data quality of clinical trials (Figure 1).

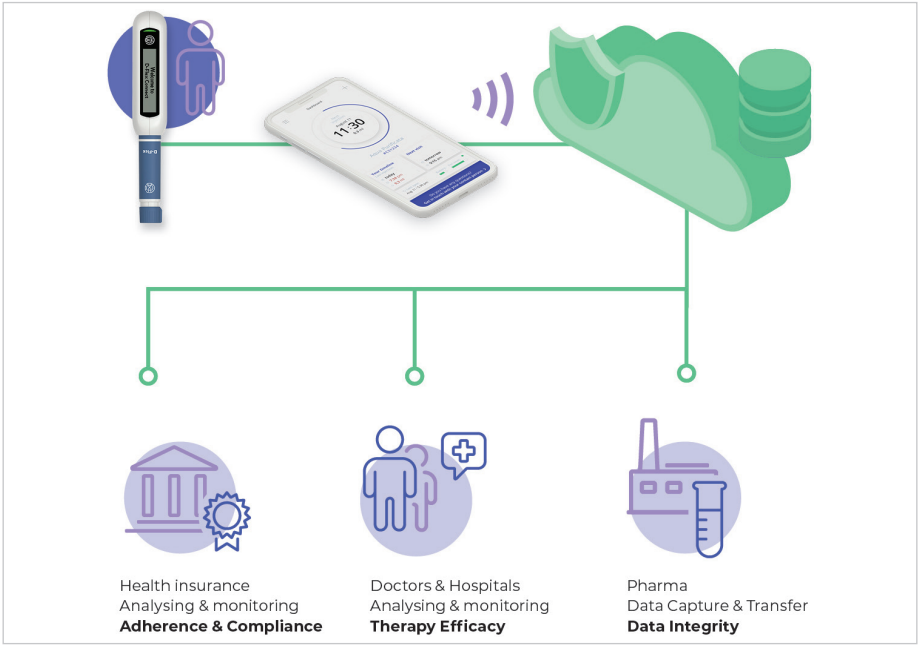

Figure 1: Adaptive data capture in clinical trials using the D-Flex® Ecosystem enables real-time monitoring and reduces the time between data collection and analysis.

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FROM DEVICE TO CONNECTIVITY

Healthcare is perhaps the best place for the application of the Internet of Things, here called Internet of Medical Things (IoMT). Connected medical devices have the potential to expand access to providers, improve the quality of care through more accurate patient information and enable patients to gain more control over their overall health. In addition, the IoMT can change the process of clinical trials, making them more efficient and cost-effective, thus reducing the time needed to research new treatments.[2,3]

Electronic data capture (EDC) in clinical trials is a contemporary way of capturing medical data digitally with the patient via an online database, instead of using the more traditional paper-based format. The case report forms (CRFs) used with EDC are called electronic CRFs (eCRFs).

eCRFs have many advantages over their paper counterparts. For example, data entry can be verified directly by the contract research organisation (CRO), which provides a better overview of patient recruitment and the quality of data entry. eCRFs also result in significantly fewer queries, as problems with illegible handwriting are eliminated. Furthermore, EDC can also be programmed with numerous plausibility checks, so that many incorrect entries, such as entering the current date instead of date of birth, are impossible.

Figure 2: The disposable D-Flex® injection pen is easy to configure for a single dose or multiple fixed dosages. It is easy to adapt to a customer's dosage requirements and ensures that a fixed dose is delivered, increasing patient safety.

The eCRF format also enables online monitoring, in which the data entered is checked for correctness and completeness, while monitoring in the study centre focuses on source data verification, i.e. the comparison of database entries and source documents. Due to the resultant time savings and its user-friendliness for investigators and study nurses, EDC has established itself in recent years to become the standard in clinical studies.

FROM TECHNOLOGY TO THERAPY

The D-Flex® Ecosystem comprises hardware, software and service-enabling data capture in clinical trials. In particular, the D-Flex® Ecosystem consists of the disposable D-Flex® injection pen, a digital cap, a mobile app and the Haselmeier data platform. The digital cap enables data capture at the point of input from the proband, patient and/or healthcare professional and subsequently the secured transfer of this data to the Haselmeier data platform. The platform works as a transient vector for transferring the captured data to healthcare provider or the CRO in their preferred eCRF format or directly into their own data system.

D-Flex® Injection Pen Product Platform

The D-Flex® injection pen product platform for use with 3 mL cartridges can be easily configured, from a single fixed dose to multiple distinct fixed doses on a single pen, bridging the gap between fixed and variable dose pens (Figure 2). The D-Flex® technology does not allow any intermediate steps between the distinct fixed doses, reducing the risk of an incorrect dose and therefore increasing patient safety.

The dose levels of the D-Flex® injection pen can be freely adjusted as part of a customer-specific adaptation programme by modifying only one component of the D-Flex® product platform. This is particularly interesting for dose-finding trials and the rapid approval and marketing of combination products for subcutaneous self-administration.[2,3]

Thus, the D-Flex® product platform offers innovative technical features that enable customers to accelerate the development of their combination product for subcutaneous self-administration by synchronising the drug development and device development processes at an early stage. In this way, device development can begin as early as Phase II trials, instead of the usual sequential start of device development after completion of Phase III trials.

The D-Flex® technology allows for optimal adaptation to the titration scheme of clinical trial design through all phases, providing important information on the therapeutic efficacy window of the drug. In addition, the technology allows for easier self-administration by the patient during the treatment phase. The handling of multiple devices, which would generally require further training or hospitalisation, can thus be eliminated, while at the same time allowing easy adaptation to the individual needs of the patient. These possibilities are of course also of increasing interest to the treating physician.

D-Flex® Connect – Data Capture and Transfer

The digital cap of the system measures the expelled dose, time and temperature; is able to transfer this data via Bluetooth Low Energy (BLE); and contains embedded firmware for its specific user interface (Figure 3). Depending on the study requirements, the app associated with the D-Flex® Ecosystem can be either minimalistic or used to collect additional data, such as patient questionnaires. The health data platform is the cloud system used to transfer

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Figure 3: The D-Flex® Connect cap works seamlessly with the D-Flex® injection pen to provide easy data collection and transfer, and facilitates analysis of data sets and dosage adjustments.

data to eCRFs, or to be used by a CRO for data validation, statistical analysis, safety and efficacy summaries, or final study reports. This means that, if desired, D-Flex® Ecosystem can provide pharma companies with an all-in-one solution, which is flexible, secure and efficient.

D-Flex® Ecosystem App

The administration-specific app transfers relevant data directly from the patient to the Haselmeier data platform, which is used primarily for data transfer to the eCRF while ensuring data security and integrity. As the mobile app can also provide essential services, such as reminders to ensure that medications are taken on time, it can also improve the patient experience. An optional feature is the possibility to enable real-time feedback from the patient if electronic patient reported outcomes (ePRO) are among the collected data points in the study. Compared with scheduling clinic visits, this can allow for faster and more regular check-ups on patients to help ensure relevant input from them, such as side effects, is not missed (Figure 4).

Mobile devices have proved to be a very useful tool for capturing data from patients in a trial, with the area of mobile health (mHealth) services seeing significant growth. Using mobile devices as a therapy management solution, patients can engage in regular surveys pertaining to their treatment and be notified about medication regimes. Additionally, other mobile capabilities, such as feedback options, gamification of the application and medication reminders, can be channelled to support behavioural change and improve clinical data collection.

If the patient does not apply the pen correctly this will be registered, and a notification can be sent via the app to ensure the correct dose of the medication is taken. This enables the organisers of clinical trials to ensure that only high-quality data and results from patients who adhered to the therapy scheme correctly are analysed, because non-adhering participants can be flagged in the system by the CRO in real-time.

Figure 4: The D-Flex® Ecosystem app not only serves to transfer data to the Haselmeier data platform, it can also improve the patient experience.

FROM CLINICAL TRIALS TO COMMERCIALISATION

Missing data and patient drop-outs in a clinical trial impacts the quality of its results and therefore its significance. Study volunteers terminate their participation prematurely for various reasons, such as side effects, lack of efficacy or because they find it simply too much effort to participate. The D-Flex® Ecosystem enables convenient digital data capture for patients at home, contributing to increased adherence, reduced drop-out rates, and a higher quality of study results (Figure 5).

The D-Flex® product platform can be easily adapted to specific customer requirements or clinical trial designs. This allows early integration of commercial device development to begin in Phase II and continue into Phase III by simply adapting the product platform. In general, only one component of the pen needs to be modified, which saves both costs and time.[4]

When setting up a clinical trial that uses connected digital devices for data collection and management, there are both opportunities and challenges for everyone involved. For starters, depending on where the clinical trial takes place, organisers must obey local data protection and data security regulations. Ethical and legal concerns regarding data collection will naturally permeate all layers of the trial. Organisers planning a clinical trial with a new medical device that allows direct data collection must consider the security of the participants' data from several angles.[5,6] Unlike the introduction of a medical device or a drug, this does not just entail whether the hardware itself adheres to the laws of the local market.

Certain questions must be answered before and while setting up the trial. The organisers must decide which data points need to be collected. Everyone involved needs to have all the hardware, software and internet access required to play their part in the trial. If participants are unable to use the device or software, is there somebody else who can and is legally allowed to? Participants have to be trained on how to use the device and/or software needed for data collection, while the medical and research staff need to know how to work with the incoming data, i.e. the software the data will be analysed with. If doctors are

Figure 5: The D-Flex® injection pen can be easily adapted to a specific customer clinical trial designs by changing just one part.

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the ones training patients to use the device or app, this will be perceived as an extra effort on their part. For this reason, it should be clearly communicated how the device or app can reduce the time and effort a doctor has to spend on a patient further down the line of a clinical trial.

In relation to data integrity,[7] points that need to be addressed before the start of the trial include the format in which the data will be saved and transferred, whether all data transfers from device to collection points are sufficiently encrypted, and who will have access to which data. Additionally, all the collected data and trial information has to be stored in a secure fashion that not only protects patients' privacy, but also follows the applicable guidelines concerning long-term data storage.

Prior to the start of data collection, roles with specific rights to view, amend and/or input data must be assigned to everyone involved. To avoid data security breaches, patient data has to be de-identified. It is important to note that the extent of anonymisation required also depends on local data security regulations. For this reason, organisers of multinational trials need to be even more careful when setting up, taking into account the requirements of regulations in effect in all the locations the trial will take place in.

Participants in clinical trials need to feel that that are being taken seriously, included, involved and informed. Uncertainty or uneasiness can lead to a lack of adherence or discontinuation. Thus, healthcare providers should ensure participants are adequately informed about how their data is used and what is done to protect their privacy, as well as reassuring them that their concerns are taken seriously. This is also important with respect to the fact that, preceding the trial, participants should agree in written form to their data being collected, stored and used for research to avoid legal repercussions for the organisers.

Analogue work processes cannot be simply transferred into a new digital environment. Therefore, a lot of processes must be redesigned to create an efficient workflow. Digital transformations take a lot of effort and it can be a challenge to get everyone onboard. New systems for data collection and management are initially perceived as a burden, adding more work. Therefore it is not sufficient to simply supply and train users with new medical devices and software without creating an awareness for the benefits for themselves. This can create an initiative that makes people want to "go digital".

FUTURE OUTLOOK

The IoMT has already begun to permeate clinical trials.[7] It is not as mainstream as it is in other sectors because the technology is still evolving and advances still need to

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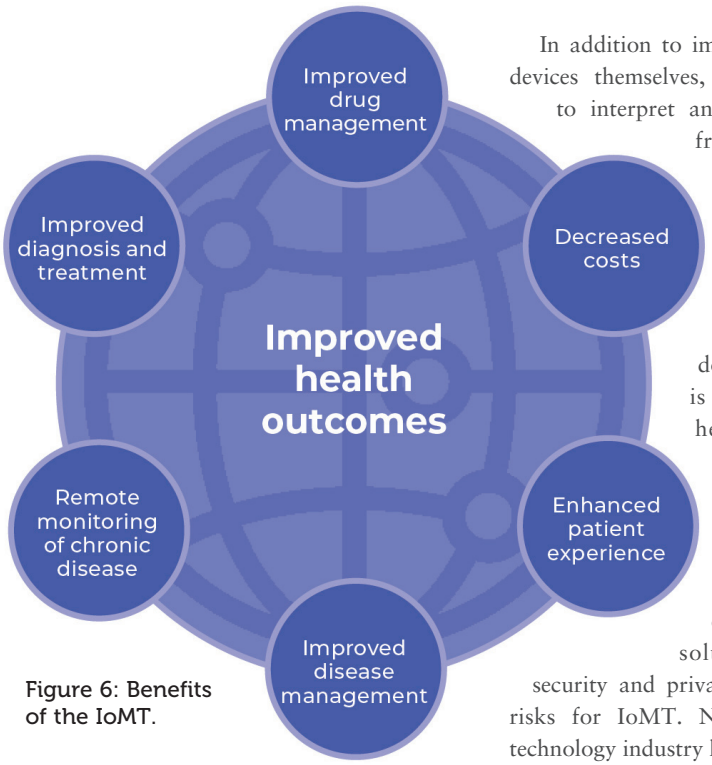

Figure 6: Benefits of the IoMT.

be made. Clinical researchers have also had a history of being hesitant to adopt new technology, as the accuracy of the data collected in clinical trials is critical and without room for error. With time, we will see its presence grow exponentially as more clinicians begin to realise the immense benefit derived from using digital devices and the IoMT,[2–4] which is significantly greater than simply speeding up data collection (Figure 6).

Of course, new technologies are not only of interest to healthcare professionals and researchers. Since some therapies can have a drastically lower efficacy if medications are taken irregularly or have to be restarted from the very beginning after a treatment discontinuation, data about patient adherence to a therapy would be of great interest to insurance providers as well. Better adherence means that there is no need to pay for an expensive treatment regime twice, after all. Having real-time access to participants' data all presented in the same format can also allow sponsors of clinical trials to be more flexible and adapt protocols or dosing schemes more easily if the need arises. At the same time, a system that collects all the relevant data without fail, and that can be accessed at any time during the trial, can be extremely helpful for the parties involved in continuous quality controls or audits. The D-Flex® Ecosystem has the potential to help monitor and improve patients' adherence to a treatment.

In addition to implementing the digital devices themselves, companies will need to interpret and use data streaming from these devices properly, with skilful data scientists and analytic tools creating value from the captured data. There is no doubt that the IoMT is transforming the healthcare industry completely by redefining how apps, devices and people interact and connect with each other in delivering healthcare solutions. However, security and privacy remain the biggest risks for IoMT. Nonetheless, since the technology industry has come a long way in providing solutions in this area, this should not be a reason not to adopt new technologies. New tools, including the D-Flex® Ecosystem, will help to form a secure integrated healthcare system with the view of ensuring patients are better cared for, healthcare costs are significantly reduced and treatment outcomes are improved.

Ultimately, remote data collection will become part of the normal therapy regime, where patients can administer drugs themselves and monitoring can largely be done via health apps and devices that measure specific biomarkers and relate patient feedback to healthcare providers. This is especially of interest in fields where patients receive care from nurses in their own homes. Having the option to document a treatment, the patients' progression and other important data points by simply transferring and saving patient data digitally, via a verified and validated system, could save a lot of time and inconvenience for healthcare providers. In theory, doctors could even provide feedback or medical advice to their patients via an app, after checking their patients' data.

Clinical-led improvement, enabled by digital technology, is transforming the implementation of clinical trials, but strategic decisions about investment in digital technology can often be a footnote in board discussions. This needs to change. These decisions need to move centre stage. Leaders in the healthcare industry need to widen their understanding of the digital health terrain and the possibilities integrated digital systems can offer, particularly to meet the immense productivity challenge ahead, and to gain practical insights, such as real-time feedback or the synchronised development of drug and device, that will help avoid expensive mistakes.

ABOUT THE COMPANY

Haselmeier, a part of Sulzer AG, has been established in the healthcare market for over 100 years. Starting as a family owned business with approximately 240 employees, Haselmeier has been pioneering the development of injection pens for subcutaneous drug delivery since the 1960s. Haselmeier continues to drive innovations in self-injection pens, from design and manufacturing to packaging and delivery. The company has developed solutions in scalable volumes for numerous pharmaceutical partners, always following state-of-the-art engineering practices – and aims to evolve even further.

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