The new value of clinical data in Europe

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Abstract
The EU's new Medical Devices Regulation and In-vitro Diagnostic Device Regulation has integrated and reinforced the regulatory requirements for pre- and post-market clinical trials and positioned them as vital to ensuring the safety and performance of a medical device on the market. These regulatory changes combined with greater access to clinical data and the technology that is now available on the market, enable manufacturers to analyse and even use clinical data in new ways. Smart algorithms can now evaluate with speed and ease a product's clinical data to benchmark it in the context of the global market for the very first time. This meta-analysis, driven by artificial intelligence, will in turn redefine the way manufacturers approach the design of clinical trials to make them more effective, efficient, reduce waste, improve product performance and safety, discover new markets, innovate devices and secure a faster pathway to funding and reimbursement.

High clinical data requirements
New regulation, technological advances, and artificial intelligence are redefining healthcare systems and medical industries around the world, but the medical devices industry is undergoing one of its most radical changes to date. Whilst producing and collecting clinical data have become more high-profile internationally, the most significant increase in regulatory requirements for clinical data has been prescribed by the European Commission's new Medical Devices Regulation (EU) 2017/745 (MDR). The effective date of the regulation has been postponed by 1 year to May 26, 2021, because of the global impact of the COVID-19 pandemic.

The MDR requires manufacturers to supply clinical data for devices both pre- and post-market as evidence of the product's performance and safety. The standards for clinical data are also higher and will apply to more medical devices than ever before in an effort to harmonise the quality of both data and devices throughout the EU. This new level of demand for clinical data presents a significant challenge for manufacturers as clinical trials are one of the most expensive and time-consuming aspects of launching a product on the market.

Small and medium-sized enterprises (SMEs), which represent 95% of medical device manufacturers in the EU,[1] are likely to be hit hardest by this new financial burden as they tend to have more limited resources, a higher dependency on a single market, and are usually more reliant on the success of a single product. As such, SMEs represent both the largest majority of manufacturers in the EU and the demographic that will need clinical evaluations to do far more than just be a vehicle to meet regulatory requirements.

The high cost and waste involved in clinical data
Generating clinical data incurs a wide variety of high and inescapable costs. Specialist knowledge, supplies, and facilities, as well as the length of time it takes to recruit for and complete a study, all contribute to the high cost of clinical trials. In 2010, a Stanford study analysing clinical data from the FDA estimated that the average cost of bringing a 510(k) product from concept to market was $31 million, but more than 77% percent of the cost (approximately $24 million) was consumed by regulatory and FDA-related activities. Similarly, the cost of pre-market approval averaged at $94 million, 80% of which was spent on the regulatory stages required to bring a medical device to market launch.[2]

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In addition to the often-soaring costs of clinical trials, investigations into clinical research practices over the years have consistently revealed a high volume of waste, with some experts finding as much as 85% of medical research is wasted globally and avoidably.[3] "This waste arises from the multiplicative effects at different stages of research: over 50% of research is not published; over 50% has avoidable design flaws; and over 50% is unusable or incompletely reported, or both."[4] Compounding this waste are issues in methodology, design bias, the misuse of statistical methods, poor reproducibility, and insufficiently rigorous studies, which in the end all amount to wasted research, resources, and time. And whilst real-world data is used for purposes such as marketing and sales we could regard it as a waste

that it is not utilised for regulatory purposes, or only very limitedly so.

Disjointed regulatory procedures waste research, resources, and time

Traditionally, pre- and post-market have been different bodies, working in separate timeframes, concentrating on different aspects of the market. It is this division between their regulatory requirements that drives the disjointed perceptions and processes that waste resources, opportunities, and time.

Pre-market, randomised clinical trials (RCTs) tend to be designed with just the regulatory requirements for a product submission in mind. Questions that relate to the clinical perspective, such as the post-market clinical follow-up (PMCF), the health tech assessment (HTA), and the quality-adjusted life year equation – all of which ultimately identify what products will receive funding and reimbursement from the healthcare system, are therefore often overlooked as they are not required for product certification. Instead, these questions are often deferred, increasing the likelihood that more data will be required later on, meaning more work and cost for the manufacturer and a slower path to funding and reimbursement.

EU MDR streamlines regulatory practices to optimise clinical data

The EU's MDR now regulates clinical investigations, integrating pre- and post-market regulatory requirements and raising requirements and standards. The MDR, for instance, requires manufacturers to support their product claims pre and post-market via post-market surveillance including the PMCF. It therefore makes sense for clinical studies to collaborate with market access studies – and vice versa – to better predict a product's economic viability as well as its safety and performance on the market.

The MDR reflects the trajectory of development in the wider world. An increasing emphasis and greater reliance on data and technology. Investors, health authorities, health professionals, and patients are demanding more conclusive clinical data, market transparency, and ultimately better and more agile health systems. This has been thrown into far sharper relief by the current COVID-19 crisis, highlighting how important data accuracy, transparency, and technology are to generating insights that enable us to implement actions with confidence, speed, and agility.

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Manufacturers therefore need to ask themselves how they can optimise the return on such heavy investments. How can the financial burden of clinical data and new technologies deliver more than the regulatory requirements for performance and safety?

The answer actually lies in the connection between the two. It is through clinical data and

advances in technology that manufacturers have the opportunity maximise the potential of clinical investigations and their evaluations.

Greater access and tech will redefine the use of clinical data

Globally, governments, policy, and regulation are increasing access to clinical data to improve market transparency, safety, and the economics involved in running healthcare systems. Primary registries, such as the FDA's ClinicalTrials.gov (which hosts over 300,000 clinical trials) and the European database on medical devices (EUDAMED) coming up with the MDR, are databases that grant manufacturers, healthcare professionals, patients, and the public levels of access to clinical data. These directives, combined with the real-world data collected by private registries, supply manufacturers with large datasets they can use to draw insights for market analysis and their business.

Technology, machine-learning, and smart algorithms are also revolutionising the way we use clinical data, shifting it from being the preserve of a highly professional sector to more public and commercial use.

For the first time in fact, the medtech industry is experiencing an excess of data generated by both traditional RCTs and new tech solutions such as health apps, wearables, sensors, and software. Produced through partnerships with tech companies, such as Zimmer Biomet and Apple,[5] and Novartis and Microsoft,[6] this new tech increasingly empowers patients to contribute clinical data independently and report the effects of a device or treatment in near-real-time.

Technology, machine-learning, and smart algorithms are also revolutionising the way we use clinical data, shifting it from being the preserve of a highly professional sector to more public and commercial use. Deep 6 AI, for example, uses artificial intelligence to locate appropriate candidates for clinical trials in "minutes instead of months"[7] by using data analysis drawn from ICD-10 codes, unstructured clinical data, pathology reports and operating notes, thereby lowering the cost of clinical investigations.[8] This initiative attracted $17 million in funding in 2019.[7]

In addition to this, COVID-19 has brought to the fore how important and valuable clinical data and health apps are to healthcare. Launching an effective contact tracing app, for instance, like the application program interface (API) solutions that Apple and Google are collaborating on,[9] is being considered as key to halting the spread of the virus and supporting a transition to the new normal after a lockdown. The desire for clinical information is also not restricted to professionals in the sector. The public want access too, as demonstrated by the publicly available COVID-NMA website, which includes a data visualisation overview of the COVID-19 clinical trials being carried out around the world to "monitor in real-time any new evidence that becomes available" and "identify gaps and deficiencies of existing evidence early enough and with an aim to help prioritizing and optimizing future research".[10]

Driving the evolution of meta-analysis

However, whilst registries and databases make clinical data more publicly available, the data itself is not necessarily actionable. Industry expertise is needed to be able to read the information recorded in a clinical trial through meta-analysis. Technical, time-consuming, and performed manually, this process can be cumbersome and doesn't usually allow for lateral insights beyond the regulatory requirements of a clinical evaluation. Clinical data are also recorded in different ways depending on the individual study format and database. So, whilst technology, machine-learning, and smart algorithms can enable us to draw insights from large datasets at speed, the data structure and quality itself still needs to be improved. Initiatives like the EUDAMED are helping to structure this data better and enable its use even further. This is the beginning of a significant shift in how we use clinical data and approach regulatory requirements, and a marked evolution in meta-analysis.

A year ago, we set out to create a tech collaboration to develop an algorithm that would provide manufacturers with better insights into their own clinical data. A smart algorithm is able to recognise, match, and analyse the different variety of data across clinical trials, databases, and languages at a speed that far outpaces traditional methods of analysis. Identifying gaps and deficiencies in a product's clinical data for regulatory requirements or otherwise benchmarking clinical data against existing RCTs.

Network meta-analysis powered by artificial intelligence can evaluate a manufacturer's clinical data to see whether their study is likely to meet the expectations of health authorities. It can

demonstrate how to improve a clinical trial or product for a more competitive edge, illuminate a pathway to funding and reimbursement, highlight a new market, or even identify a gap in the market for a potential innovation. The speed and accuracy of AI-driven meta-analysis also enables manufacturers to quickly and easily identify where to allocate their resources and improve the efficiency and efficacy of clinical trials through comparative analytics, reducing wasteful research and potentially speeding up the time it takes to certify a device.

Again, COVID-19 is starkly highlighting the vital importance of such algorithms if we are to draw real insight from the wealth of data being produced worldwide. Clinical data production is increasing rapidly. Our own algorithm has recorded a 500% increase in the number of RCTs between early March and late April, totalling 443 clinical trials across 57 countries with almost 300,000 patients enrolled. It is these vast datasets combined with the algorithms that can collect, read and analyse the information that are producing the insights we now rely on to shut down entire countries, as well as to reopen them.

Optimise the value of clinical data

Through AI meta-analysis, manufacturers now have the opportunity to question their regulatory processes and ask how they might benefit their business beyond the clinical evaluation. One of the most obvious points of which is to reassess how clinical trials could be designed to include additional endpoints that can be used downstream. For example, putting questions like the HTA or PMCF alongside pre-market RCT questions can produce data that helps to focus or influence post-market research or marketing initiatives. This frees up resources and potentially smooths and speeds up the pathway to funding and reimbursement. It also provides data that can be used to benchmark a product in the market that can help it to improve or become more competitive.

Integrating the design of pre- and post-market clinical trials will not only help manufacturers meet the EU's regulatory requirements but also optimise the resources that they are being required to invest. New technology and AI-driven meta-analysis allows manufacturers to assess clinical data with far greater speed and precision that can help them to both complete their clinical evaluation and transcend the traditional boundaries between pre- and post-market. It can benchmark products in the market, evaluate clinical trial design for regulatory purposes and reveal gaps and opportunities for innovation. AI-driven meta-analysis can discover new markets, new products, improve devices, and define a funding and reimbursement strategy. It can open our imagination and clarify our vision, enabling us to see how we can shape a more sustainable, inclusive, and healthier future.

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Conflicts of interest

The author declares no conflicts of interest.

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