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Open Source Closed-Loop Insulin Delivery Systems: A Clash of Cultures or Merging of Diverse Approaches?

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Abstract

Biomedical outcomes for people with diabetes remain suboptimal for many. Psychosocial care in diabetes does not fare any better. "Artificial pancreas" (also known as "closed-loop" and "automated insulin delivery") systems present a promising therapeutic option for people with diabetes (PWD)—simultaneously improving glycemic outcomes, reducing the burden of self-management, and improving health-related quality of life. In recent years there has emerged a growing movement of PWD innovators rallying behind the mantra #WeAreNotWaiting, developing "do-it-yourself artificial pancreas systems (DIY APS)." Self-reported results by DIY APS users show improved metabolic outcomes such as impressive stability of glucose profiles, significant reduction of A1c, and more time within their glycemic target range. However, the benefits remain unclear for the broader population of PWD beyond these highly engaged, highly tech-savvy users willing and able to engage in the demands of building and maintaining their DIY APS. We discuss the challenges faced by key stakeholder groups in terms of potential collaboration and open debate of these challenges.

Keywords

automated insulin delivery system, diabetes technology, do it yourself, inequality

Latest UK National Diabetes Audit data 2016-2017 show that only 30% of people with type 1 diabetes and 67% of people with type 2 diabetes achieved an HbA1c target of ⩽58 mmol/l (7.5%).[1] These figures have barely changed over the past five years, despite the increasing availability of ever-advancing technologies to support people with diabetes (PWD) in achieving optimal glycemic control. When taken together with blood pressure and cholesterol targets, these figures drop to 19% and 41% respectively.[1] Again, relatively unchanged for the past five years. The figures from the United States are equally uninspiring with average HbA1c among the patients in the T1D Exchange clinic registry being at 68 mmol/mol(8.4%)[2] as compared to the 53 mmol/mol (7%) recommended by the American Diabetes Association (ADA).[3] In other countries the situation is comparable although exact data are not always published.

Psychosocial care in diabetes does not fare any better. In the United States, fewer than half of the diabetes practices sampled by Barry et al[4] employ at least one behavioral health provider at an average of 0.6 full-time employee. Barry et al also state that almost half of those sampled do not have behavioral health integrated into the clinic and have not identified an internal or external behavioral health professional with a relevant expertise accessible to their patient population. They conclude that the discrepancy between American Diabetes Association (ADA) recommendations is particularly notable given that their sample "included practices that are ADA or American Association of Diabetes Educators (92%) and that are on the *US News and World Report* list of top 50 practices in diabetes and endocrinology (43%)",[4] suggesting that this

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group of practices are among the most advanced and distinguished in the field. Adult diabetes services in the United Kingdom do not have psychosocial support embedded within the multidisciplinary team, a topic discussed at an "All Party Parliamentary Group" meeting chaired by Right Hon Keith Vaz in April 2018. Furthermore, in many countries and in a substantial part of diabetes clinics and practices, newer technical medical devices, such as continuous subcutaneous insulin infusion (CSII) and continuous glucose monitoring (CGM), are not routinely being used, let alone sensor-augmented pump (SAP) or semi–closed-loop systems.

"Artificial pancreas" (also known as "closed-loop" and "automated insulin delivery") systems present a promising therapeutic option for people with diabetes (PWD)—simultaneously improving glycemic outcomes, reducing the burden of self-management, and improving health-related quality of life. However, the development of innovative technology in the traditional research and industrial environment and subsequent translation to the market via regulatory pathways to Food and Drug Administration (FDA) or CE marking of such technologies appears onerous and sluggish.

It is perhaps unsurprising therefore that PWD (and many of their caregivers) are seeking out novel ways to find the support they need, outside the usual provision of diabetes services. In the recent years there has emerged a growing movement of PWD innovators rallying behind the mantra #WeAreNotWaiting, developing "do-it-yourself artificial pancreas systems (DIY APS)," which connect existing insulin pumps and CGM sensor systems and close the loop between these devices through automated insulin dosing controlled by a "homemade" algorithm. The conversation surrounding this movement has intensified over recent months in several countries including Germany, the United Kingdom, and the United States. This has been fueled partly by the rapid growth of the (still) relatively small but not insignificant number of PWD building and using DIY APS (approximately >1000 worldwide currently), alongside the JDRF's "Open-Protocol Automated Insulin Delivery Systems Initiative" and broader engagement by key stakeholders in industry and regulatory agencies such as the FDA.

Self-reported results by DIY APS users show improved metabolic outcomes such as impressive stability of glucose profiles, significant reduction of A1c and more time within their glycemic target range.[5] However, the benefits remain unclear for the broader population of PWD beyond these highly engaged, highly tech-savvy users willing and able to engage in the demands of building and maintaining their DIY APS. Nevertheless, one cannot negate nor neglect to appreciate the legal problems that are associated with using DIY APS as these are medical products that are not approved by regulatory bodies. The legal issues are complex and differ depending on the individual role of the stakeholder (industry/medical device manufacturers, physicians and certified diabetes educators, PWDs, caregivers, DIY APS developers that are now PWD, payers, and regulatory agencies) and between legal systems/countries. Subsequently we address some of the challenges faced, without being legal experts.

Medical Device Manufacturers

The requirements that manufacturers must fulfill for product approval are in place to protect patients and physicians by providing a high degree of certainty that such products are working safely and effectively. Such requirements are regarded by some as an impediment to efficient iterative innovation in diabetes treatment technology because these requirements necessitate drawn-out timescales and are associated with high costs. On the other hand, more lax (or no such) requirements would lead to a swifter cadence of innovation, but perhaps at the cost of safety and efficacy. Thus, the trade-off: while some might regard the current requirements as a kind of blockade against beneficial technologies coming available rapidly, others might regard them as absolutely necessary safety precautions.

In view of the risks inherent to all medical products that deliver insulin, in this case with a degree of autonomy, the manufacturer of such a device must have a high level of confidence in its safety profile. While the regulatory burden is significant for these companies, it may organically ensure a higher level of safety in the ensuing products, and moreover regulatory approvals usually come with a certain degree of protection from legal action for the manufacturer and prescriber.

Health Care Professionals

When doctors have their own practice or, in particular if they are employed by a hospital, questions of liability need to be answered when they treat patients that are using a DIY APS or that express the wish to use one. As an analogy, the hypothetical case of a physician "prescribing" a patient treatment using an unauthorized drug (especially one that has never been tested in a clinical development program) is a clear-cut violation of the law.[6] Similarly, if an endocrinologist or other HCP gives therapy recommendations to a patient who uses a DIY APS, knowing that these systems are unregulated, they could become liable. On the other hand, physicians' most fundamental calling—to help their patients—may indeed predispose them to encouraging the use of these systems. Ultimately, physicians must decide individually how to weigh the sides of this dilemma, but they should be aware of the possible consequences. Legal authorities overseeing hospitals or clinics and practices will possibly look into this matter for use of unapproved medical devices in such institutions.

People With Diabetes

If PWD are aware of the fact that the DIY APS is not approved by regulatory bodies, they might not have a full understanding of what it means. In reality, there is no

liability by the manufacturer, for example, when a previously approved medical device such as an insulin pump is remotely driven by a DIY APS, should the medical device fail. If an acute emergency occurs, such as hospitalization of the patient due to an acute diabetes-related complication or should the patient be involved in a traffic accident, and the cause could potentially have had something to do with the causative agent's diabetes disorder, of course, questions will arise regarding the lack of approval of the medical product. Also, questions about treatment recommendations or treatment errors, especially when it comes to assessing liability or insurance benefits will surely arise. In Germany, for example, the costs for a treatment in a hospital might not be covered by the payers if the reason for the stay is usage of a DIY APS, that is, the patient has used an unproved medical product at his or her own risk.

Caregivers

If a third person, such as parent/caregiver, partner, or friend of a PWD, sets up a DIY APS for someone else, the setup becomes no longer "DIY." In that case, the third person could become liable. Furthermore, it must be clear whether it is the decision of the PWD or third person to use the DIY APS and whether full understanding of core issues is held by both parties.

DIY APS Developers

Although DIY APS applications and the algorithm behind these systems seem to perform well in real-world use, the set-up must be done by the individual PWD and end-user at their own risk. The systems are developed collaboratively by volunteers with a professional background in computer science and accessible open source. However, due to the unregulated and unproven safety of DIY APS, developers cannot and should not share their work as "ready to use/plug-and-play products," for example, through an app store. Were they to do so, they would become as liable as a medical device manufacturer. An advantage of DIY APS is that the device is designed specifically for an individual where the design fits the person's own specific needs. However, the device may not include regulation and safety systems now being designed for the general user, thus it is important to remember that what works for DIY developers may not work for a different, or less sophisticated, user. It is unclear where liability would lie in this regard.

Payers

In Germany, as in some other countries, the costs for medical devices are most often reimbursed by health insurance companies. Most probably these companies are not allowed to reimburse treatment costs for medical devices and supplies that are used in a DIY APS. Even if the individual component parts are approved for their intended use, their combined use in a DIY APS would, in most incidences, automatically revoke this approval. This might even go further to the point that payers might not approve medical treatment of emergencies or other complications if these were caused by an unapproved medical device.

Regulatory Agencies

Currently in all countries except the United States, there are no approved hybrid or fully closed-loop systems commercially available and/or reimbursed for PWD. The Medtronic 670G system is the only hybrid closed-loop system worldwide that has been approved by a regulatory body yet. Furthermore, closed-loop systems in commercial development are currently available only to those participating in clinical trials. It remains unclear when the FDA-approved Medtronic 670G and other systems in development or waiting for approval will become commercially available in other countries; however, this may take years depending on regulatory approval processes and issues associated with reimbursement in each country. Previous devices, for example real-time continuous glucose monitoring systems (rtCGM), have taken many years to achieve full reimbursement, for example, in Germany for all PWD on insulin therapy who are eligible. In some countries, however, rtCGM and CSII therapies are still not being reimbursed or may be available only to certain groups of PWD at high risk (such as pregnant women, young children, or PWD with hypoglycemia unawareness).

Ways Forward

There is currently an unprecedented opportunity to collaborate in traditional and nontraditional, unchartered ways to benefit the broader diabetes community. As with other technological developments, early adopters are instrumental in opening the path for others. Traditional research, with time-tested efficacy and safety pathways, is slow and poorly responsive to change. While meeting regulatory and IRB standards, accountable and rigorous, it sometimes fails to meet the needs of PWD in providing technologies that are promised to be "very close" but still in reality are too far away. The DIY APS movement is highly engaged, enthusiastic, creative, and expert in developing engineering solutions from outdated equipment. Their speed, agility, and ability to respond quickly and effectively to the needs of their community are to be commended.

The merging of these two perspectives should be explored. The JDRF's Open Protocol initiative may well play a pivotal role in that merger. A collaboration between advocacy groups, PWD, the DIY community, industry (for example Roche Diabetes Care indicates their interest to support such developments), and regulatory bodies interested in approval closed-loop systems (like the FDA has documented with the Medtronic 670G system) seeks to bring clarity to

the regulatory and liability implications mentioned above. Building on the success of the Nightscout movement, which contributed to the development of improved communication between glucose monitoring devices and remote visualization of data, adopted by industry and registered by the FDA. Many PWD are seeking a "plug and play" system to facilitate choice of individual diabetes devices working together in closed-loop systems to support optimal self-management. Such a system is premised on manufacturer training and device support, health care team best practice medical advice, and community support.

The current regulatory approval systems are based on the provision of robust, high-quality evidence and data. These data, from a medical and psychological perspective, aim to ensure that devices are fit for purpose and the benefits outweigh the risks. The FDA recently authorized the first fully interoperable continuous glucose monitoring system and is currently reviewing the pathway for similar devices.[7] This should enable developers of future systems to bring their products to market in the least burdensome manner possible. Theoretically, approval times for AP systems under development may be shortened, which may reduce the need for and associated risk of a DIY system. With the strongest will in the world, and all the technological advancement there can be, unless PWD are appropriately and adequately supported to manage the demands of the tools they have, the full potential of those will not be realized: optimal glycemic control with optimal quality of life.

We suggest an open discussion, also with politicians and policy makers, to rapidly change regulatory hurdles that block the availability of medical products from which many PWD would profoundly benefit. "We are not waiting!" is good for the (sub)group of PWD using DIY APS, but "let's tackle it!" is even better having many more PWD in mind.

Conclusion

Traditional research is proven, but it can and must learn from more dynamic, adaptive, and effective techniques used by diverse approaches. Safety is paramount, as is a level playing field for all PWD who could benefit from closed-loop systems. Let's tackle it and reduce the burden of living with diabetes by having this debate and moving forward together.

Abbreviations

ADA, American Diabetes Association; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; DIY APS, do-it-yourself artificial pancreas system; FDA, US Food and Drug Administration; HCP, health care professional; IRB, institutional review board; JDRF, Juvenile Diabetes Research Foundation; NICE, National Institute for Health and Care Excellence; PWD, people with diabetes; rtCGM, real-time continuous glucose monitoring; SAP, sensor-augmented pump.

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