



Insulin Pump Risks and Benefits: A Clinical Appraisal of Pump Safety Standards, Adverse Event Reporting, and Research Needs

A Joint Statement of the European Association for the Study of Diabetes and the American Diabetes Association Diabetes Technology Working Group

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Insulin pump therapy, also known as continuous subcutaneous insulin infusion (CSII), is an important and evolving form of insulin delivery, which is mainly used for people with type 1 diabetes. However, even with modern insulin pumps, errors of insulin infusion can occur due to pump failure, insulin infusion set (IIS) blockage, infusion site problems, insulin stability issues, user error, or a combination of these. Users are therefore exposed to significant and potentially fatal hazards: interruption of insulin infusion can result in hyperglycemia and ketoacidosis; conversely, delivery of excessive insulin can cause severe hypoglycemia. Nevertheless, the available evidence on the safety and efficacy of CSII remains limited. The European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) have therefore joined forces to review the systems in place for evaluating the safety of pumps from a clinical perspective. We found that useful information held by the manufacturing companies is not currently shared in a sufficiently transparent manner. Public availability of adverse event (AE) reports on the US Food and Drug Administration's Manufacturer and User Facility Device Experience (MAUDE) database is potentially a rich source of safety information but is insufficiently utilized due to the current configuration of the system; the comparable database in Europe (European Databank on Medical Devices [EUDAMED]) is not publicly accessible. Many AEs appear to be attributable to human factors and/or user error, but the extent to which manufacturing companies are required by regulators to consider the interactions of users with the technical features of their products is limited. The clinical studies required by regulators prior to marketing are small and over-reliant on bench testing in relation to "predicate" products. Once a pump is available on the market, insufficient data are made publicly available on its long-term use in a real-world setting; such data could provide vital information to help health care teams to educate and support users and thereby prevent AEs. As well as requiring more from the manufacturing companies, we call for public funding of more research addressing clinically important questions in relation to pump therapy: both observational studies and clinical trials. At present, there are significant differences in the regulatory systems between the US and European Union at both pre- and postmarketing stages; improvements in the European system are more urgently required. This statement concludes with a series of recommended specific actions for "meknovigilance" (i.e., a standardized safety approach to technology) that could be implemented to address the shortcomings we highlight.

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Insulin therapy by means of continuous subcutaneous insulin infusion (CSII) is an efficient and flexible method of insulin delivery that can be associated with improved glycemic management and clinical outcomes (1,2). Insulin pumps have evolved rapidly since their introduction nearly 40 years ago and are now smaller, more precise, and more reliable than their predecessors. There is growing use of insulin pumps in individuals with type 1 diabetes of all age-groups, as well as in some individuals with type 2 diabetes. The ratio of children to adults using an insulin pump appears to vary across countries. Many pumps now have dedicated meters for self-monitoring of blood glucose (SMBG) that can automatically send blood glucose readings to the pump and are equipped with algorithms for suggesting bolus doses based on user-estimated grams of carbohydrate and blood glucose level. Recently introduced systems consist of a dedicated continuous glucose monitor (CGM), an insulin pump and a control algorithm that includes a “threshold suspend” or “low glucose suspend” feature. In this way, basal insulin infusion is interrupted for 2 h if the glucose level reaches a pre-specified value and the patient does not react to the hypoglycemia alert (3,4). Increasingly automated “closed-loop” systems are being developed.

The increasing use of pumps and innovative technology have been widely welcomed by the international diabetes community. However, there are associated challenges, including potential risks to users. In this context, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have joined forces to review the systems in place for evaluating safety from a clinical perspective. The aim was not to replicate overviews of CSII therapy available elsewhere (5), but instead to consider how health care professionals, pump manufacturers, regulatory authorities, and policymakers can best ensure the safety of new and long-standing users of insulin pumps as the technology continues to develop. We gathered evidence from clinical experience, the published literature, regulatory authorities, and pump manufacturers.

It was recognized that rapid innovation in this field and the continuous introduction of new features dictate a short product life cycle for each specific

model of pump. The approaches used for ensuring device safety therefore differ in significant ways from those required for drug safety.

CURRENT USE OF CSII THERAPY

In general, CSII is a treatment option for adults with type 1 diabetes who are motivated to improve glycemic control following a trial of multiple daily insulin injection (MDI) therapy and who can show the level of self-care required for adherence. The situation is broadly similar in children, although in some countries CSII is routinely started at the time of diagnosis. Guidelines are available recommending either broad (5) or narrow (6) indications (see 3a in the text box of recommendations below). Although there is no overall consensus, it is widely accepted that those with frequent, severe hypoglycemia and/or hypoglycemia unawareness may derive particular benefit. Individuals with type 2 diabetes may be considered for CSII therapy in some countries. As CSII is more expensive than MDI, some health care and insurance systems will only reimburse the additional costs when they judge the health economic data to show evidence of significant benefit. However, other health care and insurance systems, including in the US, increasingly consider CSII to be a lifestyle choice and are adapting policies accordingly.

Rates of CSII use appear to vary greatly internationally (7,8). The total number of pump users worldwide is unknown as the numbers sold and operating are not currently reported by the manufacturers, but estimates from financial reports suggest that the number may be 0.75–1.0 million. A recent Medtronic MiniMed Paradigm and 530G pump recall included 444,374 units in the US and 293,000 patients elsewhere (9). We would consider it helpful to have a more accurate estimate of the number of insulin pumps in use to allow a more reliable calculation of the rates of pump malfunctions and human errors. More detailed information on use of the different models would also help in understanding usage patterns, tracking outcomes, and making informed estimates of treatment costs (see 2a, 4b).

CLASSIFICATION OF MEDICAL DEVICES AND REQUIREMENTS FOR MARKET APPROVAL

The various makes and models of pump available use different technological

solutions for delivering insulin. To obtain marketing approval, manufacturing companies must submit a premarket notification demonstrating fulfillment of regulatory requirements (10–13). The principal criterion is that the pump is at least as safe and effective as a “predicate” device already in clinical use. Satisfactory mechanical performance under highly controlled conditions, physical robustness (e.g., impact of water or temperature), and adequate precision of insulin delivery must be demonstrated. All those released on to the market should fulfill certain standards of precision when new, e.g., the International Electrotechnical Commission (IEC) standard 60601-2-24 for infusion pumps in the US.

In the US, the Food and Drug Administration (FDA) classifies insulin pumps as Class II (moderate risk) devices. However, those that are part of an integrated system with a CGM are classified as Class III (higher risk) devices. Class III devices are required to go through a Premarket Approval process involving scientific and regulatory review of extensive original data to evaluate safety and effectiveness. It is important to note that clinical studies are not required for Class II insulin pumps to be granted marketing authorization: manufacturers are generally only required to perform small “human factors” studies to verify that pump users can understand and properly use the device or newly introduced features. In contrast, clinical trials are required for Class III systems, but the focus of such studies is on the safety of the algorithms and functionality of the system rather than on the performance of the pump per se.

From a clinical perspective, it is clear that daily use of devices containing electronic and moving parts in a wide variety of conditions poses considerable challenges to performance. For example, the precision of insulin infusion rates over the life span of a pump might be acceptable at the time of manufacture but may not be as precise following several years of real-world use. We consider that bench testing at the premarketing stage provides insufficient information for users and health care professionals on longer-term durability in the real world (see 2d).

In the European Union (EU), pumps are classified as Class IIb. Review of

marketing applications is delegated to “notified bodies” who can exercise considerable discretion in the nature of the evaluation they require in order to grant certification (the “CE mark”). This system provides a lower level of safeguard than that used in the US against a device posing a significant risk of harm being distributed in the marketplace (14). In 2011, following highly publicized issues with nondiabetes medical devices (breast implants and hip replacements), the EU Commission urged notified bodies to act only within their areas of expertise and to exercise their full range of regulatory powers. Use of a database for sharing safety information on medical devices among national competent agencies and regulatory authorities was made obligatory (see below). Since then, there has been a strong political will to strengthen the system, but more fundamental changes have been delayed (see 1a).

ADVERSE EVENT REPORTING AFTER MARKET APPROVAL

Once insulin pumps and other medical devices are marketed, associated adverse events (AEs) or concerns can be reported either to the manufacturers or directly to the regulators: the FDA in the US or the National Competent Authorities (NCAs) in the EU (15). The FDA requires that manufacturers report and analyze spontaneously reported AEs associated with all medical devices. It has the authority to impose additional post-marketing surveillance requirements on the manufacturer. In the EU, postmarketing and premarketing evaluation is delegated to the individual national authorities.

AE reports from insulin pump users provide a potentially rich source of information for quality assurance and improving safety (see 5a). In the EU, AEs are compiled in the EU-wide database known as the European Databank on Medical Devices (EUDAMED). This database is accessible to notified bodies and NCAs (e.g., the Medicines and Healthcare Products Regulatory Agency in the UK, the Agency for the Safety of Health Products in France), but cannot be accessed by the public. We have therefore focused on the FDA’s adverse reporting system and relied primarily on the Manufacturer and User Facility Device Experience (MAUDE) database as a source of

data (www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm).

Detailed reporting is time consuming and provides no direct benefit for physicians: our analysis of MAUDE (see below) suggests that the majority of reports are submitted by users, as AEs listed contain less detail than would be expected from physician-submitted reports. In cases of pump failure or malfunction, the device is usually returned to the manufacturer for analysis, but the outcomes of the resulting investigations are not made public (see 2e).

Companies are required to share the AE data they receive with the regulatory authorities. Each has its own procedure for reviewing and categorizing incoming reports and is responsible for identifying any pattern of serious harm associated with use of its products. Much of the responsibility for ensuring safety is therefore delegated to the pump companies themselves (including companies that provide insulin infusion sets [IISs] and insulin products). The FDA has powers to react to specific concerns via a range of options, e.g., requesting the company to provide additional data, intensify surveillance, issue letters to users/physicians, or recall the device. National authorities in the EU (rather than the European Medicines Agency [EMA]) provide more limited oversight.

AE reports on the MAUDE database are publicly available and contain information including manufacturers, device brand names, and dates of reported events. However, the system is only searchable using preselected categories in a menu system rather than by user-selected keywords. It is therefore difficult to apply clinically relevant filters to reports, e.g., model of pump or demographic group affected. It is not possible to extract the types of AE that are most likely to occur at different stages in an individual’s journey of care. Moreover, it is difficult to interpret the extent to which individual events were finally attributed to device or IIS malfunction, user error, or a combination of these (see 2g).

For the calendar year 2013, our search of MAUDE produced 24,066 manufacturer and user device reports covering a wide variety of insulin pump-related issues. The menu search term selected was “pump, infusion-insulin.” It is possible that more reports are available

under additional search terms, but this phrase provided the longest list of relevant reports. In this analysis, there were nearly 30 times as many reports relating to a pump from one of the smaller manufacturers ($n = 19,564$) as there were for one of the most frequently used pumps ($n = 718$). These differences confirm that understanding and comparing reported rates of AEs is problematic: the data are not suitable for comparative analysis, but individual reports do highlight important issues that emerge in routine clinical practice.

In a published 10-year retrospective study of AEs reported to the FDA, 1,594 reports related to insulin pumps were documented between 1996 and 2005, including 13 deaths (16). Notably, the number of serious and fatal medical device AEs rose by about 17% per year between 2001 and 2009. The reason for this trend is uncertain but may be related to the expanding use of pumps. As with our own analysis, this study was uncontrolled and lacked FDA verification of the accuracy and completeness of the reported AEs (see 1b).

On the basis of our investigations, we believe that a more standardized and transparent approach to identifying, reporting, and cataloguing AEs would help both patients and health care providers to understand the risks associated with insulin pump therapy (see 1a–c). This could be achieved in large part by improvements to the MAUDE and EUDAMED systems. For example, better access to these data coded with relevant keywords could help to identify common causes of AEs and foster the development of tailored approaches to re-education and/or reassessment of suitability for ongoing pump therapy following critical events (see 3b).

Owing to the speed of innovation, small modifications are made over time to pumps, their associated software/menu systems, and the manufacturing process without undergoing clinical studies or being publicly announced. Manufacturers have to document such changes in both the US and the EU, but these data are not publicly accessible. More transparency would be of help to quantify and understand the impact of such changes on the rates of AE reports and their contents (see 2f).

The FDA has now approved two sensor-augmented pump systems and one

threshold suspend system, which are Class III systems. After approval of the threshold suspend system, the FDA also required the company to undertake a significantly enhanced postmarketing surveillance study, which will require active follow-up of all users with periodic phone survey or, in some cases, office visit follow-up. This higher level of reporting related to actual (real-world) user experience may provide an opportunity for assessing the value of enhanced postmarketing surveillance of pump use. For instance, it may determine how many button and infusion set errors, blank screens, and actual pump failures occur during use of this device. If informative, it could serve as a model for increased surveillance of Class II pumps (see 1b,c, 2c, 4b).

CUSTOMER COMPLAINTS AND PUMP RECALLS

When a user returns a pump to the manufacturer, its performance status following real-life use can be evaluated. The FDA informed us that all publicly available data from such analyses are listed in MAUDE. However, as with AEs, although some information is available in individual reports, it is not currently possible to extract a summary of the problems most frequently found and categorize them as mechanical, electronic, or related to the IIS (see 1b). In our view, an opportunity is therefore missed to glean relevant information about safety.

To supplement information available from MAUDE, we asked companies for summarized information on how many calls they receive, how they assess the incoming information (e.g., malfunction vs. user error), how many pumps are returned, and how they select what they report to the regulatory agencies. We sent a formal request seeking such information (signed by the ADA and EASD) to the manufacturers (Animas, Cellnovo, Medtronic MiniMed, OmniPod, Roche, and Tandem) on 20 June 2014. All replied promptly stating they would provide the requested information within a few weeks. By the time this statement went to press, we had received information from three companies in the form of an in-person meeting with Tandem, a conference call with OmniPod, and a PowerPoint presentation from Roche Diagnostics. From the

two meetings it was clear that no primary data on pump approval or safety data would be available, although companies were in general willing to share information on the process by which they tested their pumps, their perception of the regulatory process, and their systems for AE reporting.

We also sought information on pump and pump-related device recalls. In a search under "Medical Devices" for pumps in the FDA Medical Device Recalls database (www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm), 124 entries were found for the past 12 years. However, many of these entries were duplicates, and the actual number of discrete recalls was 10. Interestingly, most of the issues related to IISs and cartridges rather than pumps themselves (see below).

TECHNICAL ASPECTS AND HUMAN FACTORS

Many pumps offer a variety of programmable boluses according to the type of meal ingested. However, these boluses are named differently by each manufacturer, posing a challenge for education and training. Furthermore, the speed with which a given insulin bolus (e.g., 10 units) is applied once it has begun differs considerably between insulin pumps; our knowledge about the impact of such differences on metabolic control is scarce (17). From a clinical point of view we consider it important to have information on whether these enhanced features are considered helpful by either users or health care professionals as an aid to achieving good glycemic control (see 2b, 4b).

Most (but not all) pumps have the facility to receive blood glucose values directly from an SMBG meter. Provided the estimated carbohydrate content of the meal is entered by the user, this allows the pump to calculate correction doses and meal boluses according to consideration of "insulin on board." When used correctly, an insulin dose calculator can help to prevent errors by decreasing both overtreatment and undertreatment; such features claiming increased safety by thus preventing both hypoglycemia and hyperglycemia are highlighted in marketing materials. Many pump users might benefit from these, but almost no good evidence exists in support of this assumption (18). We are aware of users who appear to

derive benefit from pump therapy without being able to make full use of these features and providers who are reluctant to advocate them in the absence of more definitive supporting evidence.

An important aspect of medical device design and development is human factors engineering, which is the study and optimization of how people use and interact with technology. Over the last decade, the FDA has established clear requirements for the design and evaluation of new medical devices with respect to human factors (19). Manufacturers of insulin pumps are required to evaluate the handling of new devices by regular users rather than just engineers and highly trained laboratory personnel. These measures are intended to verify that the devices will work safely, accurately, and reliably before they reach the market. However, studies of actual everyday use are not required.

Human factors studies and analyses occur in a number of settings, including evaluation in the clinic of user performance in adjusting pump functions or inserting IISs. There will usually be a focus on a specific aspect, e.g., understanding written instructions or being able to read a display. These evaluations complement typical clinical trials, which are not sensitive to identifying or quantifying many aspects of human performance. Human factors evaluation of insulin pump systems is an important part of the FDA's premarket evaluation process. It is to be welcomed, but we believe that more studies are required to guide efforts to optimize the design of pumps according to the needs of different groups of users (see 2b, 3c, 4a).

IISs

When insulin infusion is genuinely blocked for any reason, the user needs to be warned as soon as possible because there may be only a few units of insulin in the subcutaneous depot around the tip of the infusion needle/cannula. This insulin is fully absorbed within hours, so hyperglycemia or ketoacidosis can rapidly develop following catheter occlusion if the glucose level is already elevated or rising quickly. However, this requirement is balanced by the need to minimize inappropriate warnings that may cause "alarm fatigue." Depending on the technology used by the pump and the infusion rate required by the

user, it can be many hours before an occlusion alarm is signaled, leaving the user at risk of serious harm. Inappropriate handling while changing the insulin cartridge or technical errors with the IIS represent additional sources of risk, e.g., priming the infusion set while it is connected to the user or connecting the infusion set without due attention (see 2b,c).

The number of publications focusing on IISs is small. However, many AEs on the MAUDE database relate to IIS difficulties. The reasons for occlusion vary and may relate to the frequency of IIS change, “kinking” of the catheter in the skin or of the tube between the pump and the catheter. The mechanisms underlying blockage are not well understood; it is speculated that a complex interaction can occur between the plastic material used in the IIS, the insulin formulation used, the way the insulin is pumped and the infusion site. This might be due to differences in the physicochemical stability of insulin related to the properties of the IIS. It is noteworthy that in the US, labels for the duration of insulin cartridge usage vary between products: e.g., Apidra (insulin glulisine; B3Lys,B29Glu human insulin)—new cartridge recommended every 2 days; Novolog (insulin aspart; B28Asp human insulin)—new cartridge every 5 days.

Insertion of IISs at the same skin site over and over again raises the risk of local skin reactions, including lipohypertrophy (20). From clinical experience, only a limited area of skin may remain available for catheter insertion in those who have used pump therapy for many years. There have been some case reports of lipohypertrophy/lipoatrophy in association with pump use or specific insulin types. However, there are very few systematic data on the epidemiology of lipohypertrophy in patients on CSII, including the extent to which insulin absorption from such skin areas is impaired (see 4b).

We were unable to find guidelines on use of IISs specifically with insulin pumps or on assessing difficulties associated with the long-term use of pump infusion sites over long periods of time. However, IIS issues have led to the greatest number of recalls by the FDA in the US (see above). The pump and the IIS should be considered as parts of a system rather than as individual components (21). However, this is not

currently the case, as some IISs are cleared as part of the pump system under different product codes and some are cleared as a separate device product code. AE reporting is typically coded under the assigned product code when cleared. Therefore, IIS issues might be listed on different FDA websites (see 2c).

EDUCATION AND TRAINING

Our analysis of the MAUDE database suggested that the majority of AEs relate to human factors/user error rather than to technical pump malfunction per se and that preventable AEs may occur more commonly in nonspecialized practices. Rational strategies for reducing AEs caused by user error include the following:

1. Appropriate selection of candidates for pump therapy
2. Providing those beginning pump therapy with appropriate (and ongoing) education and support
3. Ensuring that health care professionals supporting pump users are themselves well trained and supported
4. Ensuring that teams supporting pump users contain a critical mass of members with the necessary skill mix (medical, nursing, dietetics, diabetes educators) (see 5b)

REGISTRIES: SOURCES OF REAL-WORLD PUMP USE DATA

A US survey from the 1980s stated that 25% of CSII pumps malfunctioned: 29% of these malfunctions were due to drive failure and 14% due to battery issues (22). It is likely that these proportions are lower with modern pumps, but the available information is insufficient for this to be concluded with certainty.

In the US, the T1D Exchange Clinic Registry includes over 26,000 individuals with type 1 diabetes from over 70 centers across the US on MDI or CSII (23,24). It represents a variety of demographic settings and approaches to diabetes management, but covers the more skilled and experienced centers with a relatively large volume of pump usage. In a report from this registry, individuals with the best HbA_{1c} levels were more likely to be using CSII. In children, 69% in excellent glycemic control used pumps compared with 41% of those in poor control (23). Of the 627 adults in excellent control (HbA_{1c}

<6.5% [48 mmol/mol]), 54% were using an insulin pump compared with 46% in the fair/poor control group (HbA_{1c} >8.5% [69 mmol/mol]); $P = 0.001$ (23). Of 6,500 pump users who provided baseline and 1-year follow-up data, 4.4% had discontinued pump use in the past year, with a variety of reasons noted, most commonly relating to user comfort. Reported rates of ketoacidosis were similar between MDI and CSII users (24). The T1D Exchange Clinic Registry is closely allied to Glu, a US patient networking site that collects data on insulin pump use: this could also be a useful source of safety information if the data were made available for these purposes (25).

In the EU, diabetes registries containing data from all (or at least most) of the total users in the population are established in Sweden, Scotland, Austria, and Germany. Information from these registries on real-life use of pumps has been published (26); more could be extracted with greater support, e.g., on user outcomes, HbA_{1c} levels, frequency of SMBG, bolus administration, frequency of IIS changes, type of IIS used, type of insulin. Results from unselected cases from these cohorts might differ from those of clinical trials. In one survey of 640 new pumps from four different insulin pump manufacturers, 36% were reported to have a defect of some sort including 16% that had failed and 6.5% that required replacement due to a mechanical defect (27,28). To date, registries have focused on collecting data on metabolic control, but they should be encouraged to include a wider range of items in their databases, covering—among other aspects—AEs with insulin pumps. In the literature, several multicenter reports on the rate of and risk for discontinuation of insulin pumps as an indicator of patient/doctor dissatisfaction have been published (29,30) (see 4a).

CLINICAL TRIALS

Classical large multicenter clinical trials of sufficient duration to derive outcome data with insulin pumps are of limited feasibility as a result of rapid innovation and the introduction of new models during the period of study. However, there are already examples of large publicly funded clinical trials addressing clinically relevant issues (e.g., Relative Effectiveness of Pumps Over MDI and Structured

Recommended Actions

1. The regulators (EU/FDA) should:
 - a) harmonize standards to be met by pump manufacturing companies at both pre- and postmarketing stages
 - b) provide, publicize, and maintain a single publicly accessible international database (expanded from the current MAUDE system) for AE reporting. This should be searchable according to clinically relevant keywords such as demographics, user errors, components involved (hardware, software, IIS), consequences of event (diabetic ketoacidosis, hypoglycemia, etc.), and model/year of pump manufacture.
 - c) publish an annual summary of regulatory activities
2. Pump manufacturing companies should be required to provide with transparency to the regulators:
 - a) annual estimates of the number of individuals who use their insulin pumps (including basic demographic data)
 - b) the results of clinical research conducted into the human factors associated with newly introduced features of pump design
 - c) updated data on the compatibility of their pumps with specific insulin formulations and infusion sets
 - d) systematic data on the durability and precision of insulin pumping over years of real-world clinical usage
 - e) open data on the results of testing pumps that are recalled or returned
 - f) open listings of changes in device function, features, and specifications reported to authorities
 - g) fully anonymized reports of all AEs categorized according to 1b above
3. International and national professional societies should:
 - a) provide updated evidence-based guidelines on indications for insulin pump therapy
 - b) recommend appropriate forms of structured education required for new and established pump users
 - c) set standards for levels of staffing and skills required by teams of health care professionals providing initial and ongoing education and support for pump users (supporting reimbursement of these activities by payers)
4. International and national research funding bodies should:
 - a) provide or facilitate funding for well-designed independent clinical trials of safety, efficacy, outcomes, and adherence under real-world conditions
 - b) provide or facilitate significant financial support for long-term data collection within new and existing registries
5. Health care teams should:
 - a) encourage and support pump users under their care to report all AEs
 - b) provide structured training/regular updates for pump users under their care according to standards set by national and international guidelines

Education [REPOSE], NCT01616784). More funding should be made available for such trials. Care should be taken to ensure that trials financed or supported by manufacturing companies are conducted by independent investigators to minimize bias and ensure credibility (see 4b).

SUMMARY

By harnessing innovative technology, modern insulin pumps appear to provide clinically important and increasing benefits for people with diabetes. This statement aims to contribute to the improvement of pump technologies by stimulating the adoption of a more rigorous, standardized, and transparent approach to safety—namely, “meknovigilance” (from the Greek *mekhanikos*, meaning “of the nature of or pertaining to machines”). On the basis of the

evidence summarized above, we recommend the specific actions listed in the text box.

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Duality of Interest. No honoraria were received by members of the ADA–EASD Diabetes Technology Committee (AEDTC) for writing the manuscript or associated meetings, although travel costs were covered by the EASD and ADA. Most of the members of the AEDTC work with industry, as listed below; however, the industry is considered to have had no impact on the manuscript or its content by reviewers from the ADA and EASD.

L.H. is partner of Profil Institut für Stoffwechselforschung in Neuss, Germany, and of Profil Institute for Clinical Research in San Diego, CA. He is a member of a number of advisory boards for companies developing novel diagnostic and therapeutic options for diabetes therapy, including Roche Diagnostics, Sanofi, Abbott, and Medtronic. G.A.F. is President and CEO of Kinexum, which advises multiple health product companies in the fields of metabolism, cardiology, oncology, and dermatology. He was formerly Group Leader, Division of Metabolism and Endocrine Drug Products, FDA. J.R.P. has served on an advisory board for one company manufacturing medical diagnostic devices (Alere) and for a number of companies manufacturing pharmaceuticals used in the treatment of diabetes. R.W.H. coordinates the German/Austrian Diabetes Prospective Documentation (DPV) Initiative, which has been supported by Novo Nordisk, Medtronic, Roche Diagnostics, Boehringer Ingelheim, and Lilly through institutional research grants. R.W.H. has not received any personal honoraria. R.M.B. has done clinical trials and consulted or served on a scientific advisory board for Abbott Diabetes Care, Becton Dickinson, Bayer, Dexcom, Eli Lilly, Johnson & Johnson, Medtronic, Novo Nordisk, Roche Pharmaceuticals, and Sanofi; he receives no personal income from any of these activities as any payment goes to the nonprofit Park Nicollet Institute. A.L.P. has been a consultant for Medtronic MiniMed and has received a grant from the Medtronic/MiniMed Foundation. She has served as a consultant and/or speaker for multiple nondevice-related companies.

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References

1. Pickup JC, Keen H, Parsons JA, Alberti KG. Continuous subcutaneous insulin infusion: an approach to achieving normoglycaemia. *BMJ* 1978;1:204–207
2. Pickup J. Insulin pumps. *Diabetes Technol Ther* 2013;15(Suppl. 1):S24–S28
3. Ly TT, Nicholas JA, Retterath A, Lim EM, Davis EA, Jones TW. Effect of sensor-augmented insulin pump therapy and automated insulin suspension vs standard insulin pump therapy on hypoglycemia in patients with type 1 diabetes: a randomized clinical trial. *JAMA* 2013;310:1240–1247
4. Bergenstal RM, Klonoff DC, Garg SK, et al.; ASPIRE In-Home Study Group. Threshold-based insulin-pump interruption for reduction of hypoglycemia. *N Engl J Med* 2013; 369:224–232
5. Grunberger G, Abelseth JM, Bailey TS, et al. Consensus statement by the American Association of Clinical Endocrinologists/American College of Endocrinology Insulin Pump Management Task Force. *Endocr Pract* 2014;20:463–489
6. Diabetes UK. Insulin pump therapy. Also known as continuous subcutaneous insulin infusion (CSII). Position statement (updated September 2011).

- Available from www.diabetes.org.uk/Documents/Position%20statements/Position_Statement_Insulin_pump_therapy090911.pdf. Accessed 24 December 2014
7. Maahs DM, Horton LA, Chase HP. The use of insulin pumps in youth with type 1 diabetes. *Diabetes Technol Ther* 2010;12(Suppl. 1):S59–S65
 8. Beck RW, Tamborlane WV, Bergenstal RM, Miller KM, DuBose SN, Hall CA; T1D Exchange Clinic Network. The T1D Exchange clinic registry. *J Clin Endocrinol Metab* 2012;97:4383–4389
 9. Close Concerns. Medtronic issues class II recall for MiniMed Paradigm and 530G systems [Internet], 2014. Available from www.closeconcerns.com/knowledgebase/r/846b6e3d. Accessed 24 December 2014
 10. US Food and Drug Administration. Infusion pumps total product life cycle. Guidance for industry and FDA staff [Internet], 2014. Available from www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM209337.pdf. Accessed 22 January 2015
 11. US Food and Drug Administration. Draft guidance for industry and Food and Drug Administration staff - medical device reporting for manufacturers [Internet], 2013. Available from www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm359130.htm. Accessed 25 October 2014
 12. US Food and Drug Administration. Deciding when to submit a 510(k) for a change to an existing device (K97-1) [Internet], 1997. Available from www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080235.htm. Accessed 25 October 2014
 13. Council of the European Union. Council Directive 93/42/EEC of 14 June 1993 concerning medical devices [Internet], 1993. Available from http://eur-lex.europa.eu/legal-content/en/ALL/;ELX_SESSIONID=YJQGJLGd1JrpT98QbJKC8KMcchrTtQfzj1fjznyTjVv1p2vfp6bh!283099387?uri=CELEX:31993L0042. Accessed 25 October 2014
 14. Kramer DB, Xu S, Kesselheim AS. Regulation of medical devices in the United States and European Union. *N Engl J Med* 2012;366:848–855
 15. European Commission DG Health and Consumers (SANCO). Guidelines on a Medical Devices Vigilance System [Internet], 2013. Available from http://ec.europa.eu/health/medical-devices/files/meddev/2_12_1_ol_en.pdf. Accessed 11 November 2014
 16. Cope JU, Morrison AE, Samuels-Reid J. Adolescent use of insulin and patient-controlled analgesia pump technology: a 10-year Food and Drug Administration retrospective study of adverse events. *Pediatrics* 2008;121:e1133–e1138
 17. Regittnig W, Urschitz M, Lehki B, et al. Absorption kinetics of insulin following subcutaneous bolus administration with different bolus durations. *Diabetes* 2013;62(Suppl. 1):A247
 18. Heinemann L. Insulin pump therapy: what is the evidence for using different types of boluses for coverage of prandial insulin requirements? *J Diabetes Sci Tech* 2009;3:1490–1500
 19. US Food and Drug Administration. Human factors and medical devices [Internet], 2014. Available from www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HumanFactors/. Accessed 25 October 2014
 20. Blanco M, Hernández MT, Strauss KW, Amaya M. Prevalence and risk factors of lipohypertrophy in insulin-injecting patients with diabetes. *Diabetes Metab* 2013;39:445–453
 21. Heinemann L, Krinelke L. Insulin infusion set: the Achilles heel of continuous subcutaneous insulin infusion. *J Diabetes Sci Tech* 2012;6:954–964
 22. Mecklenburg RS, Guinn TS, Sannar CA, Blumenstein BA. Malfunction of continuous subcutaneous insulin infusion systems: a one-year prospective study of 127 patients. *Diabetes Care* 1986;9:351–355
 23. Campbell MS, Schatz DA, Chen V, et al.; T1D Exchange Clinic Network. A contrast between children and adolescents with excellent and poor control: the T1D Exchange clinic registry experience. *Pediatr Diabetes* 2014;15:110–117
 24. Simmons JH, Chen V, Miller KM, et al.; T1D Exchange Clinic Network. Differences in the management of type 1 diabetes among adults under excellent control compared with those under poor control in the T1D Exchange Clinic Registry. *Diabetes Care* 2013;36:3573–3577
 25. Lee JM. Glu together as one: an innovative online social network for engaging patients with type 1 diabetes and their caregivers and advancing research to improve the lives of patients with type 1 diabetes [Internet], 2012. Available from <http://medicinex.stanford.edu/jlee-abstract/>. Accessed 25 October 2014
 26. Gudbjörnsdóttir S, Eliasson B, Svensson AM, et al. Insulin pumps (CSII) and cardiovascular diseases and mortality in the Swedish national diabetes register. *Diabetologia* 2014;57(Suppl. 1):A196
 27. Guilhem I, Leguerrier AM, Lecordier F, Poirier JY, Maugeudre D. Technical risks with subcutaneous insulin infusion. *Diabetes Metab* 2006;32:279–284
 28. Guilhem I, Balkau B, Lecordier F, et al. Insulin pump failures are still frequent: a prospective study over 6 years from 2001 to 2007. *Diabetologia* 2009;52:2662–2664
 29. de Vries L, Grushka Y, Lebenthal Y, Shalitin S, Phillip M. Factors associated with increased risk of insulin pump discontinuation in pediatric patients with type 1 diabetes. *Pediatr Diabetes* 2011;12:506–512
 30. Hofer SE, Heidtmann B, Raile K, et al.; DPV-Science-Initiative and the German working group for insulin pump treatment in pediatric patients. Discontinuation of insulin pump treatment in children, adolescents, and young adults. A multicenter analysis based on the DPV database in Germany and Austria. *Pediatr Diabetes* 2010;11:116–121