

Randomized Controlled Trial Design for Simulator Use in Diabetes Education: Some Issues for Consideration

Dear Editor:

We thank Dr. Biermann for his interest in the AIDA diabetes simulator.^{1,2} He makes various observations, which it may be useful to discuss further.

As Dr. Biermann will be aware, our original protocol was published in another journal³—and covered in some detail our reasoning behind adopting the protocol that we have. However, the article ran to 17 pages, which was probably long enough for an initial description of the approach. Hopefully, we will be able to expand here. However, we recommend that these comments should be read together with the comprehensive protocol description.³

In this respect, we have considered many of the issues raised by Biermann,⁴ but for various reasons opted not to include these in our initial pilot studies. As the saying goes, “there are many ways to skin a cat.” Similarly, there are many ways that a software program, like AIDA, can be evaluated. However, while it is clearly useful to have a discussion—we think the most important thing is to actually get on and run some studies, and learn from the experience.

Connected with this it may be worthwhile to point out that there can always be a downside when designing studies in trying to do *too much*. Similarly, it is possible to have too many variables or parameters to measure, and/or too many components to a study. This can actually impact on one’s ability to execute such a trial—simply due to study logistics. Therefore, the old adage to “keep it simple” comes to mind. Given this, as we have highlighted before,³ we found it necessary in drawing up our protocol to balance what might be ideal versus what is practical, given limited time and resources.

As such, one of us (E.D.L.) has described a “pyramid of tests” that might be applied to evaluate the educational utility of a program like AIDA (Table 1).^{5,6} We are working our way through this in order to try and evaluate the program as rigorously as we can. This does take time—but the end result, if the program

passes each stage, should be a well-validated piece of software—with some evidence to support its wider educational use.

In this respect, one possible misconception that we would like to correct early on is that a single study can (or needs to) address all the possible points that one may wish to investigate with a given piece of software and a randomized controlled trial. One study cannot, and we feel it should not, do all of this. Rather, we see there being a whole series of studies, over a period of time, that will gradually address different points of interest and which will be revised and focused on particular questions that need answering. However, our hope and intention is that these further studies, by adopting a common basic protocol,³ will have some common structure that will assist later in making comparisons between studies.

Connected with this, no single study can prove efficacy. Rather, we anticipate the need for a number of studies, hopefully in increasing numbers of patients, with increasing numbers of teachers, in separate centers that will, over a period of time, both confirm the safety and establish the efficacy of using simulators in diabetes education sessions. We also expect to learn from such studies how best to apply the simulator program in different settings.

Dr. Biermann has made various statements which it might be worthwhile to respond to,

TABLE 1. DIFFERENT LEVELS OF EVIDENCE FOR FORMALLY EVALUATING EDUCATIONAL/CLINICAL USE OF A PIECE OF SOFTWARE, THAT CAN BE APPLIED TO A PROGRAM LIKE AIDA

Level	Evidence
1	Formal, open, clinical randomized controlled trials (RCTs)
2	Case-controlled trials (comparisons made but not randomized)
3	Observational studies (including surveys and questionnaires)
4	Anecdotal evidence (including independent user comments and reviews)
5	Methodological verification and validation studies

From Lehmann.^{5,6}

and discuss, point by point. Quotes from Biermann's letter⁴ are given in bold italics below.

"The authors want to use this program in the education of groups; so far, it has been used for home study." AIDA is used by people with diabetes at home and by their relatives. However, AIDA is also used by health-care professionals to teach patients as well as students. A recent survey of 1,360 downloads of the AIDA program (between November 1999 and July 2000) identified that 56% were made by patients with diabetes, 13.5% by relatives of patients, 13% by doctors, 6.5% by students, 4.2% by diabetes educators, 1.6% by nurses, 1.1% by pharmacists, and 4% by other end users who regarded themselves as none of the above.⁵ Therefore, nearly one-third of downloads during this period were made by healthcare professionals or students. Given this, one place where we think it is quite reasonable to start with the evaluation of AIDA is in a supervised hospital/clinic setting.

"Little is known, however, about the outcome of patient groups using a simulator." In one sense, this is correct—but in another, not. As long ago as 1997/1998, diabetologists were trying to use AIDA to teach people with diabetes in an educational center setting.⁷ The same reference⁷ also describes the experience of an endocrinologist in teaching medical students in a group setting. So the group approach has been tried—although the experience is relatively limited. However, we feel that one does need to start somewhere.

One issue not mentioned by Dr. Biermann anywhere in his letter is that of logistics. As intimated above, it is fine to consider the theoretical optimum study to evaluate a given diabetes computer program. Indeed, it can be useful to do so. However, in practice, rather more mundane issues of available staff and time dictate the realities of what can be achieved in a given clinical setting. Given this, we have had to be realistic as to what we can hope to manage, given no formal funding or commercial support for this work.

Clearly, the optimum study would involve randomizing a large number of people with diabetes to use AIDA on their own at home for a period of time. The control group might be given a textbook to read, or some other differ-

ent diabetes information source. At the beginning and end of the study, glycosylated hemoglobin (HbA_{1c}) levels could be measured and patients could complete questionnaires about their experience with the software and confidence with diabetes. While this might most closely mirror how the largest number of people with diabetes are currently using AIDA, this could prove very complicated to organize. Training with the computer and software would be needed. And would time spent learning how to use the computer and/or program count towards the overall time spent in the study? It could be found that the learning curve period—which may be substantial for some users—could outlast the actual period of study. In this respect, it is the experience of one of us (E.D.L.) that AIDA users are still discovering new uses for the program months after first downloading the software from the Internet. So evaluating the PC AIDA software in a home setting is not without its problems. Furthermore, coordinating things to ensure that patients who have never been seen or met by the study coordinators—most likely in other countries—have their HbA_{1c} levels measured (and validating that the self-reported data provided are honest and correct) could be very difficult, notwithstanding problems of comparing HbA_{1c} values from different laboratories using different assays.

Lest it be thought that we have not considered these issues—we have, in some detail. Probably the most realistic way of organizing such a simulator study at home would use an Internet-based version of AIDA called "AIDA online"—which is freely available at www.2aida.org/online. Visitors could be enrolled into such a study, via email and the Internet, and exposed to a Web-based tutorial about insulin-dosage adjustment and balancing insulin and diet in diabetes, with their progress through the tutorial and their use of the diabetes simulator being monitored via the Web. With the support of a home HbA_{1c} monitoring company, it should be possible to arrange for all patients who are interested in such a study to be sent a home HbA_{1c} monitoring kit—for return to a single central laboratory. Only patients who returned an entry sample for HbA_{1c} analysis would be allowed

to proceed into the study. In this way, potentially, large numbers of interested participants could be recruited—and by conducting all lessons (tutorials), simulations and questionnaires via the Web—the usual logistical problems (access to teachers, time, room space, computers) might be bypassed. For people who are interested, an introductory tutorial that demonstrates some of what might be taught on such an Internet-based diabetes simulation course can be found at www.2aida.org/tutorial

Such an Internet-based study—while perfectly feasible—is still a little way off, for various reasons (predominantly lack of investigator time). Furthermore, it could be argued that for initial evaluation studies, it makes most sense to apply the software in a semi-controlled environment with a diabetes nurse, educator, or doctor being present to answer patient queries.

An alternative way of arranging the evaluation of such a diabetes simulator could be via group teaching sessions. For some time, attempts were made by one of us (E.D.L.) to try and get these started. However, the need for multiple computers in a diabetes clinic setting was perceived as a major hurdle to arranging such a study. The scenario of a diabetologist, nurse, educator, or teacher with a class of patients—each with a computer in front of them—simply was

not feasible, as it seems (quite understandably) that diabetes clinics and education centers just do not have such spare multiple-computer capacity.

Given this, a compromise way of evaluating the educational use of a program like AIDA is to do this in small group teaching sessions. Such an approach only requires a single computer—which many diabetes centers are likely to have. Indeed, the specification of the computer required to run AIDA v4 is actually very low—so an old personal computer (PC) quite possibly destined to be thrown out could be used for this purpose. Many hospitals seem to be purchasing computer projectors (which can project PowerPoint™ and other presentations onto a large screen). Such a computer projector could be used equally well for projecting AIDA's diabetes simulations onto a big screen. Alternatively, we have found that things work just as well to connect two standard display monitors to a single computer. This can be arranged via a very cheap (Super) Video Graphics Adaptor (VGA/SVGA) monitor signal splitting device. In this way, three patients can follow each screen, and each participant can have a good view of the simulation curves. Another method of achieving the same effect is to run the simulation software on a notebook PC and connect this to an external monitor (Fig. 1). Many mod-



FIG. 1. One possible seating arrangement for participants during a diabetes simulation lesson. In this example, a notebook computer—running the AIDA software—has been connected to an external computer monitor, giving all participants good views of at least one of the displays. (Due to privacy rules about photographing patients, the people seated in this photograph are nondiabetic subjects who have volunteered.)

ern notebook PCs allow a "slave" external monitor to be connected, and in this way—as shown in Figure 1—six subjects can easily get to see one of the computer displays, close up.

This approach seems to have overcome the hurdle of lack of access to multiple computers in a diabetes clinic—and therefore has allowed us to embark on gaining further experience with the use of AIDA for teaching in a diabetes education setting. Furthermore, this approach does not require the participants to be computer literate. Rather, this only requires the teacher/facilitator/"wizard" who is leading the class to know how to use the computer (and AIDA)—so that there is no added learning curve of the technology for the participants.

It is important to stress that we do not regard such a study as being the "be all or end all" of evaluation using AIDA. Rather this is just a first randomized controlled trial step on what may turn out to be a long road to rigorously evaluate the software.

Looking to the future, it could be that some diabetes charities or diabetes companies might be willing to provide improved computer facilities to a few select diabetes education centers to evaluate some diabetes software more closely. However, we expect that such support could be dependent on seeing some evidence of efficacy before funding such experimental ventures. In this respect, there is so much that *could* be done with an educational diabetes simulation program like AIDA. However, most successes with AIDA to date have been achieved by taking lots of small steps in the desired direction—rather than by trying to achieve great leaps forward in one go.

"Only reports about individual use are available except a study in our own center looking at a few patients through the measurement of patient satisfaction. There are, however, no medical outcome parameters." With AIDA/AIDA online, we have a growing range of experience with use of the software from a wide variety of people with diabetes—as well as their relatives and health-care professionals and students—in a range of different settings.⁵⁻¹³ In addition, last year we completed a preliminary randomized controlled trial, based on our published protocol,³ using the PC AIDA software with 24 insulin-dependent

(type 1) diabetic subjects.^{14,15} The preliminary results were presented at the American Diabetes Association Annual Scientific Meeting in Philadelphia in June 2001,¹⁴ and medical outcome parameters are available from this study.¹⁵

Briefly, the study showed that HbA_{1c} levels dropped significantly in the diabetes simulation group from 7.2% to 6.4% after lessons with AIDA ($p = 0.01$). By contrast, no significant changes in HbA_{1c} were observed in the control group between baseline (7.1%) and the end of the control group lessons (7.0%), or the end of the cross-over phase lessons (6.8%). In addition, the number of symptomatic hypoglycemic episodes ("hypos") decreased significantly from 31 to 14 in the diabetes simulation group ($p = 0.03$) after AIDA lessons, but did not change significantly in the control group from baseline ($n = 20$) to after the control lessons ($n = 22$). However, the number of hypos did decrease significantly (to $n = 10$) in the control group after exposure to the diabetes simulator during the cross-over phase ($p = 0.03$ vs. 6-week data).^{14,15} Larger trials are clearly needed, but we believe this study does demonstrate the feasibility of using a prospective randomized controlled trial approach³ for the evaluation of educational diabetes simulation software, such as AIDA. Further information about this preliminary evaluation study can be found at www.2aida.org/evaluate on the Web.

"What is the purpose of such a simulator?" Our short answer would be that AIDA is intended to assist with diabetes education—in particular, allowing users to gain experience of different clinical diabetes situations which may be new to them.

"Is it the same as learning from books with the purpose of speeding up the acquisition of knowledge?" No—hopefully, AIDA users will gain experience and confidence about diabetes from using the program.

"Is it similar to that of a drug, that is, to relieve symptoms or to prolong life (via a reduction of a surrogate parameter such as HbA_{1c})?" No, the program is purely intended for education—to help people help themselves. The program is not meant for therapeutic use. Nevertheless, it is hoped that by enhancing educational opportunities and perhaps by achieving patient

empowerment, improvements in HbA_{1c} levels might be obtained.

"Will it have an economic effect, with the potential of reducing workload, time, and expenses for education; if so, will it result in the same medical outcome parameters, and will it replace education by self-instruction?" No. The program is not a replacement for any sort of patient instruction or education. Rather, the software is intended to offer a supplement to existing diabetes facilities. In this respect, as has been shown by the Diabetes Control and Complications Trial (DCCT),¹⁶ tight blood glucose control matters—and we know that regular clinic visits really can improve metabolic control/HbA_{1c} levels and outcome. However, it does not seem that the resources required to provide the levels of care seen in the DCCT are widely available. Perhaps using information technology (IT) and computers we might be able to offer enhanced care to a larger number of people with diabetes.¹⁷ Therefore, the intention is very much to supplement existing resources and facilities—to improve care further—rather than to try and replace any facilities (which we think would be misguided and foolhardy).

"If a simulator is handed out to patients, for example, via the internet, for self-learning at home, the program is a learning tool, in contrast to programs that claim to mirror the metabolism of an individual patient and to give real dose recommendations." We agree AIDA is simply a learning tool—nothing more and nothing less. Just to be clear, AIDA does not claim to mirror the metabolism of an individual patient and does not give dose recommendations. As an aside, we are not aware of any programs that are currently able to reliably mirror the metabolism of a wide range of individuals with diabetes (certainly with minimally invasive use—e.g., calibrated using home self-monitoring blood glucose data).

"We do not perform randomized clinical studies on books for diabetic people; the market tells us if it is good or bad." We agree that we do not perform randomized controlled clinical studies on books, but as we have tried to highlight above, AIDA is not intended to provide book-type knowledge. There is evidence in the literature that improving knowledge in

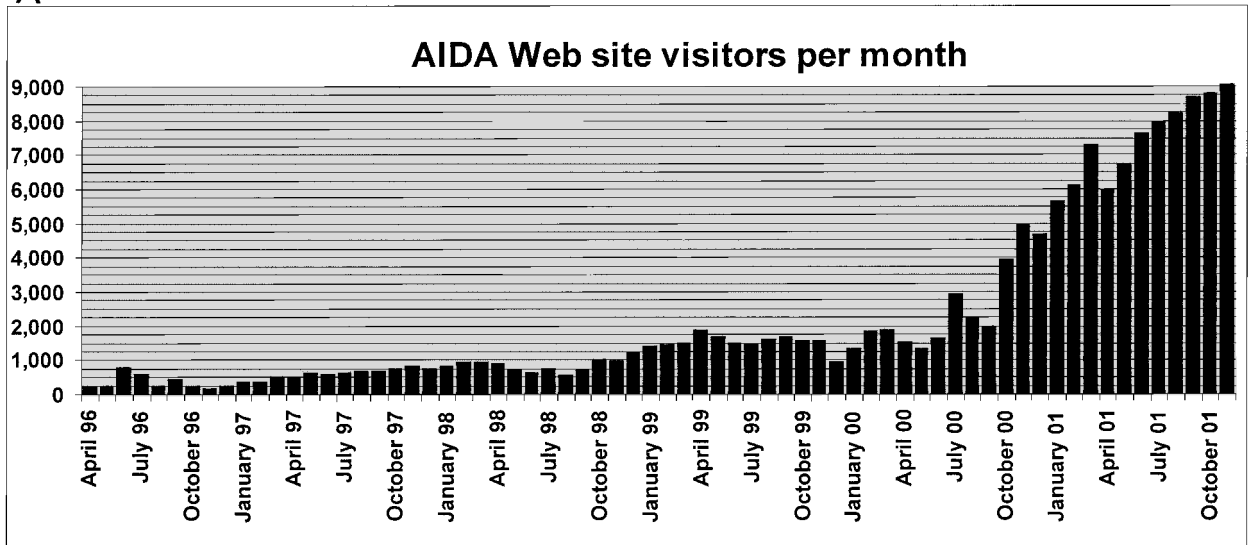
diabetes care does not necessarily actually improve metabolic control.¹⁸ Therefore, it is not book-type knowledge that we are trying to offer with AIDA. Why try to reproduce excellent books in a computer program? AIDA is meant to allow people to gain experience and learn practical things, interactively, that they cannot maybe learn so well from books.

Regarding the market telling us if something is good or bad—this is only partially true. Judging by the interest shown in AIDA on the Internet, the market seems to be telling us that AIDA is good. For instance, the AIDA Website currently averages up to 1,000 downloads of the software each month, with over 150,000 site visitors and over 30,000 copies of the program downloaded to date (Fig. 2). The continued downloading and usage of the program—even though it is now somewhat dated—seems to indicate market approval. Furthermore, the number of comments received from AIDA users (overwhelmingly positive) that have been published now approach 200,^{6–13} which seems like quite a vote of confidence in the software. But we need more evidence to support usage of this program, over and above just such anecdotal accounts.

"Neither the market nor a clinical study is able to decide if the knowledge obtained from a book or a simulator is sufficient or not." No single study will be able to decide this. However, as one of us (E.D.L.) has outlined previously elsewhere,^{5,6} there are a series of studies that could be undertaken to properly evaluate an educational computer program like AIDA (Table 1). These range from verification and validation studies, to randomized controlled trials—with less structured methods of assessment (questionnaires and surveys) also included. We are working our way through this range of studies to try to gain experience with using AIDA in different settings and also to more rigorously evaluate the possible educational benefits of the program.

"If any evaluation is required for such a home-used program, I can only imagine doing it with a questionnaire to assess patient satisfaction." We do not agree. It behoves system developers to formally test out their software. In fact, it is the experience of one of us (E.D.L.) over many years of doing work and research

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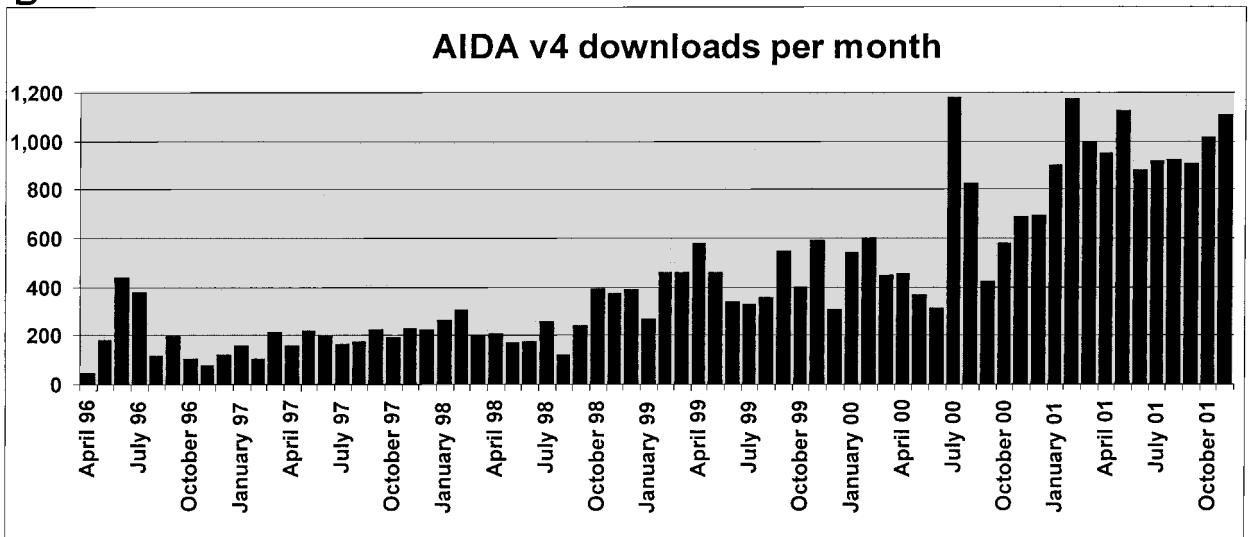


FIG. 2. AIDA Website usage (logstats) graphs for the past 5+ years (April 1996 to November 2001, inclusive). (A) Number of AIDA Website visitors per month during this time. (B) Number of AIDA v4 downloads per month. Key dates for AIDA on the Web: March/April 1996, AIDA v4.0 first released via email and the Internet for initial beta-testing. June 1996, AIDA v4.0 goes on general freeware release (following beta-testing). July/August 2000, AIDA v4.3 made available first for beta-testing and then on general freeware release. October 2000, AIDA moved to its own dedicated Website at www.2aida.org February 2001, AIDA online moved to its own dedicated Website at www.2aida.org/online September 2001, AIDA online version 2 launched at www.2aida.org/online

in the diabetes-computing field¹⁹ that, while many prototypes are developed, relatively few seem to be used more widely. A common reason for this appears to be that the prototypes' developers never take the time and trouble to rigorously validate and evaluate their programs.¹⁷ As a result more cynical, skeptical, or

less believing colleagues often remain unconvinced as to the real utility of a particular program. Sometimes the program may be used by a few developers and their close contacts—but, apart from this dedicated core group, often the software is not used further afield. It is our opinion that, in order to convince a wider au-

dience as to the clinical or educational benefits of a particular piece of computer software, we must conduct convincing and rigorous evaluation studies. We are certain that randomized controlled trials—conducted in multiple centers with multiple teachers—are the gold standard method of establishing real efficacy. Questionnaires to record patient satisfaction, which we have generated for AIDA,^{20,21} while of interest, cannot be a replacement for such formal, rigorous studies.

“Programs with individual parameters and dose recommendations”—proper discussion of dose recommendation programs is really beyond the scope of this communication. AIDA does not offer any insulin-dosage adjustment advice—and is not intended for therapeutic use. A discussion of some of the issues surrounding the application of such prototypes can be found elsewhere in the literature.^{22,23}

“It will thus be exciting to see what the first randomized trials with this class of [dosage-adjustment] programs will reveal if their real competitors—structured education with training in dose adaptation—are assigned to the control group.” Such studies comparing insulin-dosage adjustment advice programs with structured education and/or educational software would be of interest. However, before comparisons are made, it would seem sensible for both the dose-adjustment programs and the structured education/educational software to have been rigorously validated, independently, themselves. Unfortunately, as intimated elsewhere in this letter, evaluation work in the diabetes-computing field seems to trail development work by a long way. Therefore, considerably more effort needs to be devoted to validation and evaluation efforts before such prototype tools can be considered for adoption into routine clinical practice.

“Because it is not easy to visualize the physiology of insulin’s action, simulators can be included in lessons where transparencies, slide shows, or posters are normally used.” This is exactly what we have been doing: incorporating basic pathophysiology information into workshops and lessons using AIDA.²⁴

“[Simulators] are optimal for illustrating the answers to questions from patients.” We agree. AIDA is very much used as an interac-

tive blackboard to answer questions from patients (and/or students) and to stimulate discussion during the education sessions.

“Depending on the group size, more or less costly technical equipment may be necessary.” As highlighted above, we have found that a simple PC connected to two computer displays/monitors offers a very low-cost method of running these group lessons. For a whole range of reasons, as outlined elsewhere,^{3,20} small group sizes actually are preferred for these sessions.

“If a simulator is used in combination with structured education or in a combined therapeutic program, (including education and therapy optimization), it may be the focus of a randomized trial.” Randomization is simply a method used to reduce bias. Therefore, within ethical limits, most studies can be randomized, especially those where there is no risk of patients missing out on some proven or beneficial intervention as a result of the randomization process. We believe that randomization of patients (or students) to educational sessions either using AIDA/AIDA online or receiving some other educational intervention is perfectly reasonable—and offers a gold standard method of evaluating the educational utility of the program being assessed.

“Should economic aspects be included in the study design?” We think not. There seems to be a keenness amongst some workers to identify the potential economic and financial impact of prototype computer systems, before anyone has actually shown that the prototypes work or do some good. If a program cannot be shown to be efficacious (in whatever manner deemed appropriate), then economical issues become irrelevant, in our opinion. How can a nonefficacious program be an economic alternative to some efficacious intervention? Therefore, we prefer to establish the medical/clinical/educational efficacy of AIDA first, before considering financial or economical issues.

Incidentally, there may be some confusion over the terminology introduced by Biermann. He refers to medical outcomes as equating with “effectiveness,” while he suggests that economical aspects equate with “efficacy.” We do not agree. We regard efficacy as the same as effectiveness: demonstrating a positive medical

outcome. By contrast, economics considers cost-benefit analyses. Therefore, a diabetes education program may be efficacious (i.e., medically effective), but uneconomic. However, we believe that cost-benefit analyses are best done after medical effectiveness/efficacy has been conclusively demonstrated.

"They have not included economic aspects." Well, actually we considered them, but concluded that economic aspects are not relevant until we can show some measurable educational benefit from using AIDA. Basically, until we can show some improvement in medical outcome, there seems little point concerning ourselves with relatively complex financial issues, which will anyway be out of date by the time any such study is completed, analyzed, and published.

"That would comprise the question, if the six lessons and their preparations are equally time consuming." We are still learning how best to apply AIDA in educational sessions. Therefore, we may discover during the course of a series of evaluation studies—with a range of different teachers in different centers—that maybe more than six lessons (e.g., eight) are actually required to derive optimum benefit from the simulator. If this were to happen, then assessing the economic impact of six lessons could turn out to be a waste of time, as the economic assessment would need to be repeated for eight lessons. Furthermore, although this may take time, the intention is to eventually run a whole series of studies. Is it really necessary to run economic assessments with each one? We think not. Far better we believe to rigorously establish how best to make use of the software and formally evaluate the program in this way. Once efficacy has been demonstrated, then we can consider economic issues if there is continuing interest in this approach.

"Hardware and software expenses for the simulator group should be taken into account." As intimated above, hardware costs are tiny. Most diabetes centers and hospitals in developed countries will be able to find a spare, old personal computer or two somewhere. Also, the software is free, so there are no software expenses. The only other ancillary costs are for the teacher's time (for preparation and to run the lessons) and a venue to hold the class (with light-

ing/heating costs). However, these ancillary cost apply equally to an educational session run with pen and paper (or a whiteboard/blackboard) as they do to a computer-based teaching session.

"One could imagine, that even if the glycated hemoglobin will not be different in the two groups after the study, a faster knowledge acquisition may convince patients, healthcare professionals and decision-makers of our national healthcare systems [to use a computer-based approach]." We disagree. This is the often quoted argument of computer software authors, but we think the logic is flawed. To convince healthcare professionals, decision makers, and national healthcare systems to adopt a particular computer-based approach requires evidence of efficacy/medical effectiveness.

Evidence that people might be able to learn a bit faster is not really that groundbreaking. Perhaps having regular diabetes lessons more frequently could achieve the same result, without needing to purchase additional computer equipment and train people how to use and maintain it.

"If medical outcome parameters are included, the criteria for enrolling diabetic individuals should be carefully selected, for example new onset diabetics may be omitted, because the HbA_{1c} drop is present just by using insulin and in absence of any education." We agree. That is why we published our inclusion and exclusion criteria for this study *a priori* last year,³ before embarking on any trials, so there can be no confusion as to the sorts of patients to which this approach applies. For our pilot study work,^{14,15} we have been recruiting patients with diabetes of more than 6 years' duration in order to avoid any issues with newly diagnosed patients and the diabetes "honeymoon period."

"And for diabetic people with a longstanding disease, regardless whether conventional education is given or a simulator is used, Tatti and Lehmann should realize that almost any contact with a healthcare professional, specialised on metabolic problems, will result in a drop of HbA_{1c}, if elevated (or, if the glycated haemoglobin is low, with a reduced frequency of hypos)." Of course we do realize this; that is

why we have adopted a randomized controlled trial study design, so the placebo effect (or Hawthorne effect, as it is often called) will be observed in the control group as well as in the intervention group.¹⁵

"We have learned from this study [a telecare study], that the key questions should be: which subgroup or method has more benefit or which one has the same benefit at less costs?" As explained above, cost is not an issue with AIDA, as it is free. However, we have embarked on an ongoing process of workshops^{21,24} and evaluation studies^{14,15} to establish the optimum way of applying the simulator in diabetes education sessions.

"What is the rationale for the cross-over design? If a drug acts while it is taken for example to lower cholesterol and it is replaced by a placebo or another drug, a cross-over design will be helpful. The effect of six lessons, however, will hopefully not end with the last lesson and the results of the cross-over phase are unlikely to produce reliable results." The *a priori* starting point (null hypothesis) for this work is that neither intervention is likely to lead to a significant effect on HbA_{1c} levels or the number of hypoglycemic episodes. Therefore, it is perfectly acceptable to test out a cross-over study design, certainly until we obtain some data to the contrary—that is, we will not know of any confounding effect until someone actually does the study.

In this respect, we have adopted a partial cross-over design for this study. That is to say that after randomization and the 6-week course of lessons, the control group crosses over (after a 4-week washout period) to receive the active intervention (AIDA) for a further 6 weeks. The reasons for this have been discussed in detail elsewhere.³ However, briefly, we wanted to maximize the number of patients who could be exposed to the diabetes simulator and therefore the sample size/statistical power of the study. A previous observation from reviewing earlier attempts at computer-based diabetes education evaluations^{3,25} is that most suffered from lack of statistical power due to small numbers. Therefore, we sought, as far as possible, to avoid this problem with our evaluation of AIDA. Furthermore, adopting a partial cross-over design ensures that all enrolled patients

can be offered the novel (active) intervention—which is what some of them might be particularly interested in. In addition, it should be highlighted that, if the control group received significant benefit from the standard educational sessions (e.g., by reducing the HbA_{1c} level or the number of hypoglycemic episodes), then this would simply serve to make our task harder in finding a difference later between this phase of the study and the active intervention (AIDA) phase. Our limited experience so far, with our preliminary (pilot) study involving 24 patients, has not shown this to be a problem.¹⁵ However, we accept that in larger, multicenter studies it may prove necessary to discard the partial cross-over phase purely for logistical reasons, but, in fact, this would simply serve to reduce the sample size exposed to the diabetes simulator.

Regarding long-term versus short-term effects, before we can consider the long-term effect of six diabetes simulation lessons, we need to demonstrate a short-term effect. In this respect, if we do not see a short-term effect, then it is hard to imagine how a long-term effect could be achieved, unless the participants continued using the simulator on their own at home after the end of the formal study.

Therefore, we believe "first things first." We have chosen to focus initially on establishing if lessons with the diabetes simulator produce a short-term effect, before concerning ourselves with possible longer-term effects. However, in the future we are also interested to investigate—in a possible "open" phase of the trial—what the role might be of encouraging longer-term use of the AIDA simulator, by study participants, after the formal end of the main randomized portion of the trial. While this seemed to happen informally after our preliminary (pilot) study,^{14,15} with participants wanting to make further use of the program themselves at home, formalizing this process so that HbA_{1c} levels are recorded from all subjects, say, 6 months after the completion of the main trial will need to await further studies.

"I would recommend to include economical aspects in this excellent designed study and to keep in mind that the difference in real medical outcome parameters may not be as significant as it would be expected at first sight." For the

reasons outlined above, we do not believe that time spent focusing at this stage on economical issues would really be time well spent. Also we do not think that economical results can be any substitute for real medical outcome data. However, the preliminary medical outcome results that we have obtained so far have been very encouraging.^{14,15} We accept that these data are only from a small number of patients, and therefore larger-scale studies are required. We hope to embark on a medium-sized randomized controlled trial with more teachers in more centers in Italy during the course of 2002.

"I would suggest to reconsider the cross-over design, because the previously acquired knowledge cannot be deleted and the results may be questioned while the efforts for this arm may be significant including to convince patients to join another six lessons with similar content."

We do not agree. A study with a partial cross-over design will always require separate analysis of the data from the cross-over period as compared with the main randomization phase. Therefore, it will be clear from comparing the two analyses whether substantially different results are being obtained. Our initial (preliminary) experience with this approach suggests that this is not a problem.^{14,15} Furthermore, the partial cross-over design permits paired statistical analyses to be performed on the cross-over data—offering greater statistical power for these comparisons.

CONCLUSION

To date, much effort has been directed towards biological solutions for diabetes care, with emphasis on physiology, pharmacology, and epidemiology. However, there is another whole world that is rapidly expanding and that is approaching diabetes from the biophysical sciences side, with treatments trying to utilize engineering, material sciences, and informatics. All these novel approaches need to be rigorously validated and evaluated to gain the confidence and acceptance of more mainstream diabetes carers.

In the diabetes-software field, experience over the years has demonstrated that attempts have been made with various computer proto-

types to assess them medically—but when the medical evaluations have not been so impressive, reports seem to have fallen back on discussions of other considerations to report some success. We prefer to focus on establishing the potential medical/clinical efficacy of AIDA, as we firmly believe that if the medical/clinical/educational benefits can be objectively demonstrated via well-conducted randomized controlled clinical trials, then other (economic) issues can be addressed later.

We are testing out the AIDA program for small group educational use first, but longer term our vision is to evaluate individual use of the software—either on multiple PCs in a clinic (if suitable sponsorship/funding can be found to provide multiple computers) or by patients themselves at home. Economical issues will vary enormously depending on how these approaches are applied. Also, it will be important to differentiate between the economics of a study situation where equipment may be specially provided and time spent collecting and analyzing data, and the economics of routine clinical application using existing equipment in a diabetes education center.

As the logistics of running studies at home are more complicated and involved, it seems to make sense to progress onto such home-based studies only if initial studies in a hospital/clinic setting show positive and encouraging results. Therefore, we are very much taking a step-wise approach to the evaluation of AIDA. In this respect, the software cannot be evaluated by one single study, in a short period of time. Rather, a whole series of studies are likely to be required, over quite a length of time.

Finally, while we are convinced that information technology will have something to offer clinical diabetes care in the long term—being a "devil's advocate"—we also recognize the need to convince skeptics/nonenthusiasts. For this, we believe that evidence-based randomized controlled clinical trial data really are the only way to progress. However, we accept that what can actually be achieved with this evaluation approach will be dependent on how much diabetologists/endocrinologists, diabetes educators, and nurses are able to help. In particular, the degree to which clinical colleagues are willing to assist (by running lessons

using the software and collecting data to assess outcomes) will largely determine the extent to which the software can eventually be fully evaluated.

SYSTEM AVAILABILITY

The latest release of AIDA (v4.3a) can be downloaded without charge from www.2aida.org. The program runs on IBM PC or compatible 80386/80486/Pentium-based machines and requires approximately 3 Mb of hard disk storage space. The software can also be used on Apple Macintosh computers running PC emulators such as Virtual PC or SoftWindows. A fully Internet-based version of AIDA, called AIDA online, is also available for use free-of-charge at www.2aida.org/online. This allows AIDA's diabetes simulations to be run from any computer, anywhere, provided it has an Internet connection and a graphical display. An interactive educational Diabetes/Insulin Tutorial that has been integrated with AIDA online can also be accessed without charge at www.2aida.org/tutorial. This allows visitors to dynamically simulate some of what they have learnt in the tutorial about balancing insulin and diet in diabetes, using AIDA online. People who wish to be automatically informed about future updates and enhancements to the AIDA/AIDA online diabetes software range can subscribe (for free) to the AIDA diabetes simulator announcement list by sending a blank email note to subscribe@2aida.org. Any readers who might be interested in collaborating by teaching in their clinics using AIDA or by applying a standardized randomized controlled trial protocol^{13,20} in an evaluation of AIDA in clinician, specialist nurse, or educator-led patient teaching sessions are invited to contact one of the authors. Further information about the evaluation of AIDA for patient use can be found at www.2aida.org/evaluate.

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