

## INTERVIEW

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# Effective trials in diabetes: a pediatric perspective

## Diabetes Management



### **Nandu KS Thalange\* speaks to Daphne Boulicault, Commissioning Editor:**

Nandu graduated from King's College London in 1988, intent on a career in pediatric endocrinology. After junior doctor posts in and around London, he went on to a research post in Manchester, studying patterns of normal and abnormal childhood growth. After his research years he moved to East Anglia as a Senior Registrar. He undertook a fellowship in public health as part of his training, gaining experience of epidemiological analysis, needs assessment, treatment

appraisal, business planning, etc. After completing his training in Cambridge, Nandu returned to Norfolk Health Authority as lead for children's services in Norfolk, prior to taking up a post as a pediatric endocrinologist in Surrey. In 2002, he returned to the Norfolk & Norwich University Hospital. With his public health/health management background, Nandu became a clinical governance, and complaints reviewer for the Commission for Health Improvement, and subsequently the Healthcare Commission. His interests in child public health and governance led to him being appointed as chair of the Norfolk Child Death Overview Panel, responsible for scrutinizing all deaths of children in Norfolk, until stepping down in December 2012. Developing this theme, Nandu led a patient safety project looking at how to improve acute care of children coming to the Norfolk & Norwich Hospital's Children's Assessment Unit, focusing on key standards and overcoming significant obstacles to implementation. Nandu has never been satisfied with a purely clinical role, and is active in research – predominantly in conducting multicenter randomized control trials. He has been chief investigator for two major international trials of new long-acting insulins in children. These led to insulin detemir being licensed worldwide for the treatment of children as young as two years of age and more recently, insulin degludec has just been approved throughout the European Union for children over a year of age, with further approvals anticipated in 2015. Despite his wide interests, Nandu manages a substantial clinical workload, seeing children with diabetes and a range of endocrine, metabolic and related problems. His work in diabetes is recognized nationally and internationally.

**Q** Bias in trial recruitment is an important issue & efforts have been made to overcome bias within diabetes research. What are some of the exciting & clinically relevant findings that have resulted from this work?

Inevitably, clinical trial participants differ from the general population with diabetes. In my experience, the biggest difference is the level of commitment and motivation – children in trials are generally enthusiastic about participating. This is all

### KEYWORDS

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- real-world studies

\*Jenny Lind Children's Department Norfolk, UK; and Norwich University Hospital Senior Lecturer, University of East Anglia, UK; Tel.: +44 (0)1603 286357; [nandu.thalange@nuh.nhs.uk](mailto:nandu.thalange@nuh.nhs.uk)

the more remarkable given the burden of visits, venepunctures and other interventions, such as 8-point profiles. That said, the BEGIN 3561 trial was very diverse, including 350 children, aged 1–17 years, from 72 sites in 12 developed countries, with just under a quarter of children younger than 6 years of age. Of the 363 children approached for BEGIN 3561 trial, only 13 were excluded – principally because of high HbA1c (>11%). Other exclusions included children with recent ketoacidosis or severe hypoglycemia (within 3 months), non-Type 1 diabetes, or use of oral hypoglycemics. In general, I think the trial population did reflect the wider population of children with Type 1 diabetes.

**Q** Age-related bias is another topic that has been garnering increasing attention, & data from your BEGIN YOUNG 1 trial have led to EU approval of Tresiba (insulin degludec) in children & adolescents. Why is it important to represent all age groups in diabetes research? The biggest bias as far as treatment of children is concerned is that they have in the past been excluded from clinical trials, resulting in off-label use. The BEGIN 3561 clinical trial was a regulatory trial, mandated by the US FDA and EMA, and was designed to address this historic deficiency, and, as I have already said, included very young children – 85 children were under 6 years of age, including 5 from our own center. Remarkably, the study recruited down to 12 months of age. Historically, recruiting very young children just was not done – leaving unlicensed drugs to fill the treatment vacuum. Older children and teenagers were also well represented in the BEGIN study.

**Q** What are some of the differences between age groups in terms of diabetes management? Diabetes management in children varies hugely; at one end of the spectrum, we have the toddler, and at the other, the young adult, aspiring to independence. These ages bring their own challenges. Starting with preschool children – they are a particular challenge, as they have hugely variable patterns of eating and exercise, coupled with frequent illnesses, and – to all intents and purposes – no hypoglycemia awareness. It is not surprising that young children have high rates of both hypo- and hyperglycemia, and hospital admissions are much more common.

The primary school child starts to spend more time away from parents, and increasingly starts

to do some basic diabetes care such as blood tests, and – in time – insulin shots. By 8 or 9 years of age, most children are doing their own blood tests and insulin injections, but of course they still need supervision and guidance – particularly with adjusting insulin for food and exercise. The secondary school child has to contend with many challenges – including the physiological and psychological demands of puberty, coupled with the demands of coping with a chronic disease during an immensely challenging time. The diabetologist has to change his or her role from instructor, as with younger children – to coach – even when that means seeing youngsters taking the wrong road, as many do.

**Q** There has been a move toward real-world studies, to increase the effectiveness of research. Can you outline the difference between these & randomized controlled trials & their design?

There are enormous financial pressures on the NHS, and consequently it is very difficult to introduce new drugs into clinical practice, particularly if there is a significant acquisition cost. While new therapies might ultimately save money through reduced short- and long-term complications such as acute hypoglycemia or diabetic kidney disease, these benefits are often hypothetical. Historically, this has often been tackled by seeking to limit use to niche groups – in the case of insulin, this might be individuals at high risk of hypoglycemia – but paradoxically, these individuals are typically excluded from clinical trials. The deficiencies of this approach has increasingly led to the development of real-world trials where, typically, a small patient group is identified, with continued funding subject to close auditing of outcomes. If the hoped-for outcomes are indeed realized, this is persuasive to payers that wider use might be justified. Increasingly, health economists are willing to incorporate real-world trials into their analyses of cost–effectiveness.

**Q** What are some of the problems associated with the design & implementation real-world studies and their resulting data?

The principle problem in the design of real-world trials is that they are typically locally funded, and limited in scope. In consequence they are usually underpowered and relatively insensitive. Treatment groups are often heterogeneous, controls are historical or extrapolated from

untreated patients. As a result, outcomes are often not generalizable, and due to small sample sizes usually not statistically testable. This can be overcome by using research methodologies such as cross-over studies, but the regulatory burden imposed by conducting a formal research study usually precludes this approach.

**Q Recently, results from the first real-world trial of Tresiba™ (insulin degludec) were presented. Can you summarize these results & their importance?**

The data from the real-world Tresiba (Novo Nordisk A/S, Bagsvaerd, Denmark) studies are very encouraging, in that – at least in the selected groups of patients treated – the anticipated benefits, such as reduced hypoglycemia and HbA1c have been realized – usually with significantly lower insulin doses and high levels of patient satisfaction. Unfortunately, I doubt this will translate into significant uptake in use of Tresiba in the UK unless we see favorable assessments from NICE, especially given the negative opinions from the Scottish Medicines Consortium and the All-Wales Medicines Group.

**Q How far & in what way do you foresee real-world data being incorporated into future studies in diabetes in the next 5–10 years?**

I think the use of real-world studies needs to be incorporated into the design of pharmaceutical drug development programs, and, at least for drugs with a potential high budget impact, will increasingly be seen as essential. The cottage industry of small-scale audits and trials needs to be supplanted by more formal studies with adequate power, supported by health economic analyses to demonstrate that the benefits seen in homogeneous clinical trial populations are translatable to everyday clinical care.

**Q The application of technology, including wearables & smart phone applications, to medicine has been another topic of discussion. What advantages do these technologies represent in terms of trial design & data collection?**

In pediatric practice, we are increasingly using continuous glucose monitoring systems, usually in patients on insulin pumps. The wearable glucose sensors such as the Dexcom G4 offer great comfort and security to parents of young children by obviating the very real fear of severe hypoglycemia. With the advent of the

new Medtronic 640g insulin pump, and glucose sensor, with built-in low glucose suspend, we are seeing the first tentative steps toward a viable artificial pancreas. For patients not on pumps, the complicated math required to calculate insulin doses can be daunting and the use of ‘smart’ glucose meters that can calculate doses, such as the Accucheck Aviva Expert, is a real boon – particularly for the older child. Mobile phone apps that offer the same functionality are increasingly available, and with the advent of Bluetooth and other device-to-phone communication, data transmission between devices will facilitate this further.

Increasingly, mobile phones are being touted as insulin-pump control devices and glucose sensor readers, making use of the enormous computing power that underlies a modern ‘smartphone.’ Abbott’s Freestyle Libre is a very exciting development – it is an interstitial glucose monitor that gives a glucose reading when the sensor is scanned, offering many of the advantages of continuous glucose monitoring, without the downside of annoying alarms – a real turn-off for teenagers. Launched at a breakthrough price, it offers consumers a finger stick free, glucose-testing future, and Abbott has seen unprecedented demand, with orders currently outstripping Abbott’s ability to supply glucose sensors.

**Q What challenges will be associated with their application?**

All technology presents challenges – not least to professionals unfamiliar with these breakthroughs. With increased use of insulin pumps we have created the situation where many healthcare professionals find themselves challenged by the patient’s greater knowledge of their device and its management. This issue is likely to increase with the advent of increasing patient use of technology, driven by advances in biosensors and mobile phone technology. These developments are likely to be in the consumer sphere, rather than the tightly-regulated healthcare product sector, and are likely to be fast-moving and driven by user demand rather than professionals’ perceptions of need.

These technological developments represent both a threat and an opportunity to the NHS. Diabetes, much more so than many other conditions, is highly amenable to development of assistive technology and telemedicine opportunities. The threat – as ever, in the current

NHS – is the fear of increased costs. The reactive and instinctively negative reaction of NHS organizations to developments such as the advent of social media deprives patients of the ability to interact with their healthcare team in the same way they communicate with family, friends and increasingly, businesses.

**Q** Do any of these technologies, recent or forthcoming, have you particularly excited?

For me, as a pediatric diabetologist, I am most excited by the artificial pancreas, though other developments such as ‘smart insulin,’ (glucose-sensitive insulin), or perhaps stem cell transplantation may, in time, obviate the need for the artificial pancreas. The technological breakthroughs we are now seeing – better pumps and glucose sensors coupled with even faster-acting rapid insulin analogs – mean that a truly functional artificial pancreas is within reach (assuming it is affordable!), with Medtronic, Animas and other companies likely to bring such products to the European market by the end of 2017. I

would love to see diabetes take much more of a back seat in children’s lives, allowing more children to grow up unscathed – physically, or psychologically – by the diagnosis of diabetes.

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*The opinions expressed in this interview are those of the interviewee and do not necessarily reflect the views of Future Medicine Ltd.*

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