Translational Research The Way Forward:

The Diabetes Story

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THE MAN, Professor B.O. Osuntokun

Professor Benjamin Oluwakayode Osuntokun, was born on 6 January 1935, over 76 years ago, but that simple statement does convey the near pre-birth tragedy of both mother and child. When Kayode's mother, Elizabeth Otoola Osuntokun, was six months pregnant, she became critically ill. At that time, if a woman died with a visible pregnancy, the tradition was that she would be tied to a tree, in a virgin forest, above ground, in an erect posture, and left to die ignominously. Elizabeth's husband, David Osunwenu Osuntokun, out of love for his wife and in an attempt to save her life, consulted the leading native doctors of the time to terminate the pregnancy. Thankfully, all these attempts failed.

With nowhere to turn, and his wife now in a coma, David Osuntokun sought help from God through Joseph Babalola, the founder of the Christ Apostolic Church. As soon as Apostle Babalola entered their home, Elizabeth awoke from her comatose state shouting "Alleluia". Miraculously, Benjamin Oluwakayode Osuntokun was born three months later.

Amazingly, my own birth is also a product of divine intervention. My parents had been devastated by the loss of their first two children due to unexplainable causes (now

understood to be sickle cell disorder). At that time, they encountered the same Apostle Joseph Babalola who declared prophetically that the next child they would have would survive, and live, and would be of international repute and would bring them great joy and prestige. I hope I have fulfilled his prophecy. Incidentally, my mother was also named Elizabeth!

As a child, Benjamin Osuntokun was precocious. By his sixth birthday he had read the Bible in Yoruba from cover to cover. From his early youth, he had always subscribed to the tenets of the Holy Scriptures. His choice of profession was in pursuit of obeying the injunction of his Christian faith to serve others, convinced that medicine offered him the greatest opportunity to serve his fellow men.

In the same way, he attributed his success as a scientist to the support and blessing of God Almighty and hoped his career would encourage his own children and his students to go further and higher and deeper than he had been able to reach.

Benjamin Osuntokun married Olabopo Adepeju, an equally brilliant classmate from medical school, both of them graduating with four distinctions from the University of London in 1961. Olabopo, a professor of ophthalmology at the University College Hospital, Ibadan, was passionately described by Kayode as the architect of the complete domestic bliss and felicity he experienced in their home. In more colloquial terms we would say she was the 'sugar in his tea' and the 'wind in his sails'. As he said, if he came to the

world again he would marry her again and again and again and again! Their union was blessed with five children (two are medical doctors) and many grandchildren.

A gregarious and outgoing person, Kayode was surrounded by a loving nuclear and extended family, which included many high achievers — cabinet ministers, ambassadors, statesmen, state ministers, academicians, and businessmen.

During his lifetime he drew much inspiration from his teachers, professional colleagues and former students, and enjoyed much happiness and satisfaction in seeing his former students make giant strides in life, with well over forty of them holding various professorships. His friends are simply too many to number, he was a truly remarkable man.

Professor Osuntokun, a product of the famous Christ's School Ado-Ekiti, was as prodigious — suffering from a disease not uncommon amongst members of this audience and my good self, called 'multiple diplomatosis' with 24 degrees and fellowships including 4 doctorates to wit; MD, PhD and two DSc (three by examination) — as he was prolific, having published 65 original papers in the neurosciences and 321 peer-reviewed papers.

Of particular interest to today's lecture is his seminal thesis on the neurology of diabetes. He was the external examiner for my MD (Lagos) thesis on the role of glucagon molecular heterogeneity in diabetogenic states. His grasp of molecular biology humbled me.

He contributed to the professional and academic development of the University College Hospital and the University of Ibadan as Chief Medical Director and Dean. He was also an examiner for the Royal and West African Colleges of Physicians and a distinguished adviser in neurosciences to WHO.

A Fellow of the Nigerian Academy of Science, his golden achievements were rewarded locally with chieftaincy titles and nationally by the prestigious honour of Officer of the Order of the Federal Republic (OFR) and our own 'Nobel' prize, the Nigerian National Merit Award (NNOM).

Our hero was snatched away into eternity at the tender age of 60, having achieved in one lifetime what many distinguished people could not achieve in 60 lifetimes. Today's lecture is dedicated to his profound contribution to the art and science of diabetes.[1]

TRANSLATIONAL RESEARCH, THE WAY FORWARD: The diabetes story

Diabetes mellitus is a rapidly growing public health problem, and poses a great health burden to the entire world. However, most people with diabetes live in developing regions like ours.[2] The prevalence in Nigeria is estimated at 4.7% while the average in Africa is 3.8%. A total of 13.1 million people in Africa have diabetes and this is projected to double by 2030.[2] Its burden is due to the chronicity of the disease, and the development of multiple organ damage and failure, which results in a significant loss in quality of life and earning potential, as well as a high on-going medical expenditure.[3] In the year 2009, over 79,000 deaths in Nigeria were attributable to diabetes, while the total African mortality was 332,000.[2] Less than 20% of global diabetes expenditure occurs in developing regions. In Africa, an average of US$111 is spent per person. In Nigeria it is barely US$47.[2]

As a result of the diabetes burden, a huge amount of clinical research has been done to identify an effective means of prevention and management of the disease. Examples include the DCCT, UKPDS and Steno-2 trials, with the aim of achieving a significant reduction in burden and an improvement in the quality of life of people with diabetes.[4-6]

Despite the availability of this vast body of evidence-based knowledge, invariably published as 'care guidelines' or 'standards of diabetic care', the global report for diabetic care is still poor, with ever-widening gaps, particularly in the poor countries, where there are no standards for data collection. These gaps in care are due to complex barriers that are poorly understood.[7]

Therefore, the process of 'translating' evidenced-based knowledge into everyday clinical practice has now become a critical step, if we are going to change outcomes for the millions of people living with diabetes in Nigeria, and other developing countries.

The purpose of this paper is to expose what translational research is, its vital role in improving diabetes care and how we can begin the process of better translating the available evidence-based practices into everyday care.

What is Translational Research?

Basic science research is often the place of discovery of many of the useful diabetes care interventions and medications utilized today. After their discovery, a rigorous evaluation process is carried out through clinical trials, first on animals, then on healthy individuals and patient volunteers. Finally, larger patient populations are tested through before any 'breakthrough' discovery is made available for the everyday care of diabetes patients. This is often referred to as, 'bench to bedside', 'etiological research', 'efficacy research' or 'Phase 1 translational research'. In this phase, the

intervention must prove to be able to produce significant benefits. Many of these efficacious forms of intervention are archived in medical literature and standards of care documents, and are often unused.[8,9]

'Phase 2' translational research or 'effectiveness' research evaluates the utilization of this evidence-based care in everyday clinical practice.

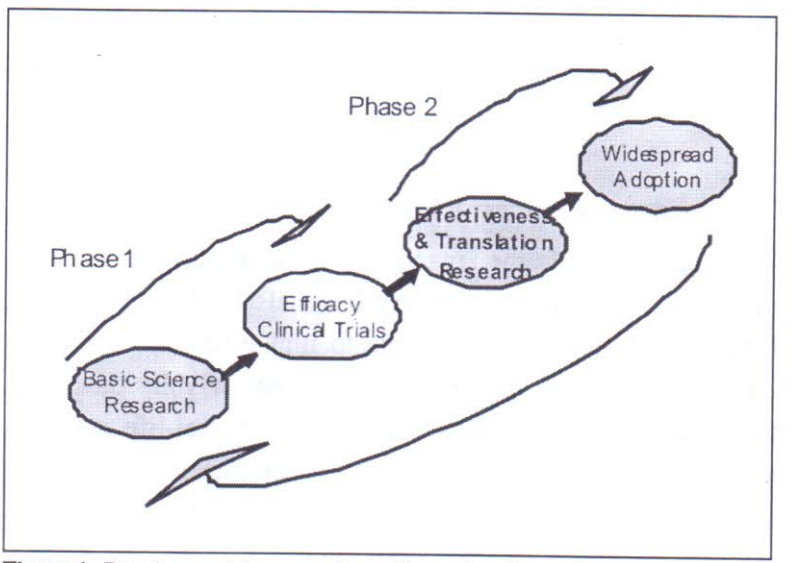

Figure 1. Developmental process for evidence-based practice

For the purpose of the rest of this paper, Phase 1 will be referred to as efficacy research and the second phase of translation of knowledge into practice is what will be referred to as 'translational research'.

Some of the fundamental differences between Phase 1 and Phase 2 translational research are:

1. Research setting: Controlled versus real-life

The many randomized controlled clinical trials that produce evidence-based diabetes guidelines are executed under very tightly controlled settings, with strict patient selection criteria that hardly reflect the populations faced by clinicians in everyday practice. In real-life settings, a wide range of factors come into play, that influence outcomes. Most of these factors are often excluded in efficacy research. Examples include patients with complications, financial limitations, lack of access to medications, education and language barriers.

2. Manpower resources: Infinite versus finite

A comparison of the manpower resources available in primary care practice or tertiary hospitals to those deployed in phase 1 research, for example to implement the intensive lifestyle protocol of the DPP trial,[8] reveals vividly the huge differences between available resources in real-life settings versus those made available for evidence-generating clinical trials.

3. Patient compliance to care interventions

Selection criteria in evidence-generating trials favour individuals who are well motivated to comply with the intervention under evaluation for various reasons. In real-life settings, whether in Nigeria or in developed countries, such compliance may not be guaranteed for a host of reasons, ranging from psychological barriers to epileptic access to drugs.

4. Skilled versus less skilled professional involvement

Often, because of the excitement surrounding novel interventions, and the benefits of participation in such trials, much attention is given to such by higher skilled care providers, as against the routine work of daily or weekly clinical practice.

In addition to the problems of resources, cultural differences and patient compliance are problems associated with reaching underserved and less-educated populations with these interventions.

Why is Translational Research Needed?

One would have expected that when ground-breaking research is published, the actual value of the new discovery would by itself generate wide-range acceptance by both providers and patients. However this is not often the case. A simple case example is the understanding that if patients sustain good glycaemic control, diabetes complications will be prevented. Yet widespread good glycaemic control is not the case. Tertiary hospitals in Nigeria have at best 30% of patients controlled, and over 30% with HbA1c > 10%, with only 52% of patients having foot examinations annually and 75% being prescribed aspirin therapy.[11]

The belief that if people are aware of better practices, adoption of the practices will automatically follow is not true. Sadly 'awareness does not guarantee adoption'. Awareness is a necessary first step, but the challenges practitioners face in everyday practice must be overcome for adoption to effectively occur.

The gap between available knowledge and practice of knowledge is wide and is believed to be getting wider by the day. A complex array of barriers hinders the implementation of new innovations. These barriers include:

- cultural practices
- education
- access to care
- health systems
- provider time constraints
- lack of policies
- funding
- need for behaviour change in patients and providers
- organizational politics
- inadequate use of information technology
- patient understanding and acceptance
- social and family support
- organization of care and so on.[8]

Translational research is the means by which we can identify these barriers and find effective ways around them. *The question is who is willingly to take responsibility to ensure that evidence-based practices are APPLIED to improve health?*

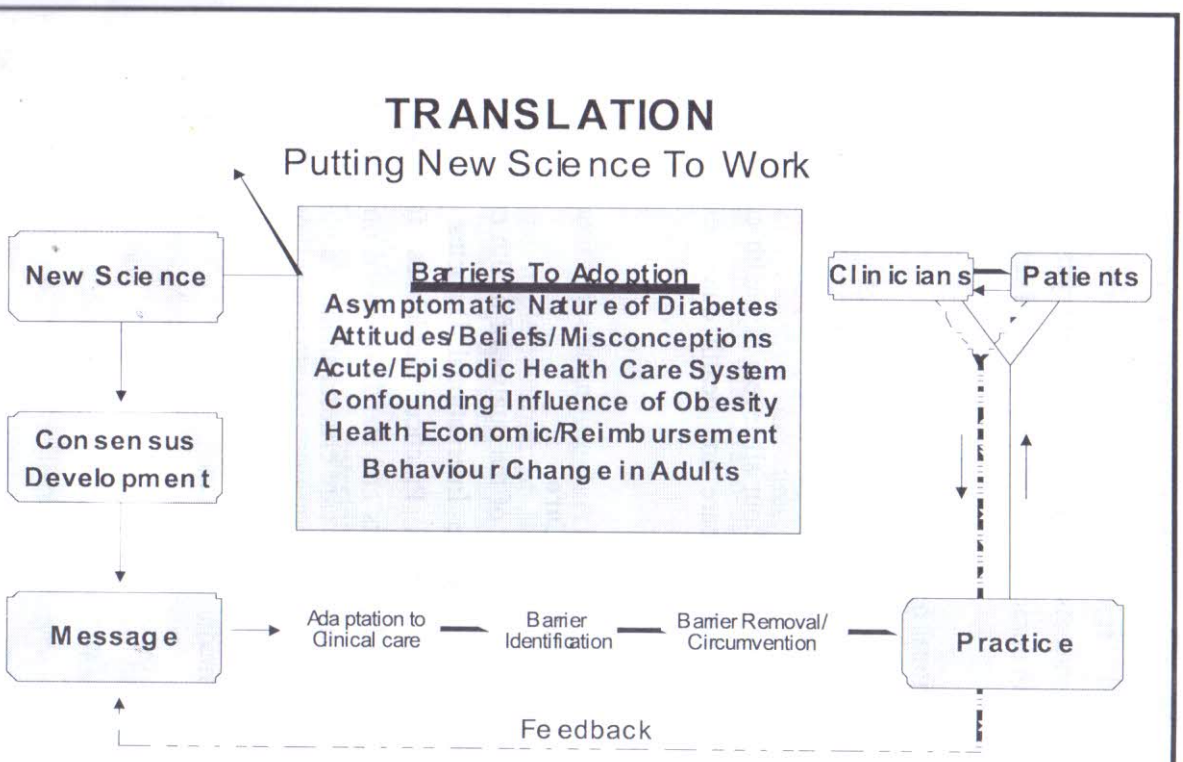

Figure 2. Conceptual framework of translational research[5].

How Do We Translate Knowledge into Care?

Translational research transforms currently available knowledge into useful measures for everyday clinical and public health practice. This is achieved by a three-step process.

Translational research aims to:

(1) *assess implementation* of standards of care

(2) *understand the barriers* to their implementation, and

(3) *intervene* throughout all levels of health care delivery to improve quality of care and health outcomes, including quality of life.[8]

Assessing the Gaps in Care

A periodic measurement of the quality of health care delivery is recommended by the International Diabetes Federation, Africa Region Clinical Practice Guidelines for Type 2 diabetes. Utilizing targets and standards based on national or regional guidelines, four care criteria should be measured:

(1) Processes of care

(2) Intermediate outcomes

(3) True outcomes

(4) Risk factor control.[12]

Processes of care include blood pressure measurement at every visit, foot examination, proteinuria screening, and

education. These are presented as a percentage of patients screened annually or educated.

Intermediate outcomes are measured as the percentage of patients achieving targets for measures such as HbA1c, fasting blood glucose, blood pressure, lipids, etc.

True outcomes are the measurements of the incidence of diabetes complications — stroke, limb amputations, blindness, end-stage renal failure — in the target population.

Risk factor control measures, among others, the percentage of patients who are overweight, obese or who exercise.[12]

Identifying and Understanding Barriers

Barriers to the implementation of standards vary, and the degree of impact of different barriers is often unique to communities.[7]

Barriers are often identified and understood through the effective use of structured interviews and focus group discussions with community representatives.[13] This forms the basis for development in patient-centred diabetes care. An example of the barriers identified is provider perspective of insulin as a last option, which is probably partly responsible for late initiation of insulin therapy.[14] While barriers like pain, fear, guilt and embarrassment play significant roles in the non-acceptance of insulin therapy by type 2 diabetes patients,[15] barriers like poor organization of care and lack of resource support and commitment to improve care by hospital

administrations have also been identified to play significant roles.[16]

Identifying, Designing and Testing Interventions

Identifying successful models and practices that can be tailored to our environment is vital to moving forward. This requires close engagement with the community to understand how best to implement them.

The literature presents a number of best practices and interventions that have successfully improved outcomes. Examples of such interventions are diabetes self-management education, and nurse case management to improve glycaemic control.

Of particular interest is the chronic care model as an intervention. The model combines several interventions and has been shown to be highly successful when implemented. The different interventions cut across provider care, patient support and healthcare delivery and the use of information technology to monitor outcomes.[17]

Research Methodology Considerations in Translation Research

Experimental design

Typical efficacy (Phase 1) research utilizes randomized, controlled designs. In Phase 2 research, non-randomization is a better study design. Non randomization creates a real world setting because the researcher has little control over the

process. However, where randomization is used, it should be above the level of the participant, e.g. randomization of care centres, hospital populations or communities.[18]

Qualitative and quantitative observational research designs should be used to identify barriers, and interventions developed to overcome them within cultural paradigms. Qualitative research designs involve structured interviews, and focus group discussions while quantitative research involves measurable data gathered through questionnaires.[13]

Exclusion criteria should be few if not non-existent. This ensures that the various types of patients that exist in real life settings are appropriately included.

Overcoming barriers to implementation of evidence-based care mostly involves a change in the behaviour of the patients and the providers. Thus, a significant portion of translational interventions will need to measure behaviour change and should thus be built using a behavioural change framework.[19,20]

Measuring Outcomes

In interventional studies, the primary aim is to see if significant improvement occurs as a result of the intervention. Thus measuring *change* is the focus, and the parameters being measured must be sensitive to the change being evaluated. Measures of change are covered in the RE-AIM concept; Reach, Effectiveness, Adoption, Implementation and Maintenance.[22,22]

Translational research needs to move beyond the measure of the effectiveness of a single outcome, to multiple outcomes. This is because there is no single best outcome measure. Rather it is important to measure from several different perspectives as different stakeholders and decision makers are interested in different outcomes to be able to interpret results, and take action where appropriate. Thus measures relevant to patients, purchasers, clinicians, and policy makers should be considered.

As the outcomes often measured in translational research are diverse, ranging from clinical outcomes to quality of life, economic indices and behavioural change, multi-disciplinary collaborations will be required to ensure validity of the research design as well as results.[23]

The importance of measuring various outcomes is seen in the adage, 'What gets measured gets done'.

The Way Forward in Nigeria; Areas of priority

To begin to change the outlook for diabetes in Nigeria, we need significant improvement in the quality of diabetes care through the successful implementation of evidence-based care. However, to develop successful change interventions we must start by measuring and documenting the quality of care. This forms the backdrop against which any improvements will be measured. The next step is to accurately identify the most critical barriers to quality care, before we can intervene successfully and identify the best interventions.[24]

The change we want to see is still some distance away, however, if we are clear on 'The Way Forward' then we can take the necessary steps in the right direction.

Successful Translational Research

To succeed, translational research must identify and understand diverse barriers, as well as promote change across several different categories of people. For such to occur, successful collaboration will need to be created across different disciplines. Community and patient participation must be solicited. The typical research methodology of efficacy research will have to be abandoned for a less controlled real world setting. And most importantly, when successful behavioural change interventions are found, these will also need to be promoted widely to prevent them getting lost in the same manner as evidenced-based knowledge does.[25]

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Dr. Kuku is also a trustee and a distinguished Fellow of the National Postgraduate Medical College of Nigeria. He is a past president and trustee of the West African College of Physicians and President of the Pan African Diabetes Study Group. A past Chairman of the Committee of Pro-Chancellors of State Universities and Committee of Chairmen of Federal Tertiary Hospitals, he was a recipient of the First Distinguished Alumnus Award University of Lagos in 1991; Ambassador of Goodwill Award, City of Freetown; first African Honorary Fellow of the Colleges of Physicians of South Africa and the Royal College of Physicians of Glasgow. He is a Fellow of the Nigerian Academy of Science. Dr. Kuku is a recipient of the National Honour of Officer of the Order of the Federal Republic (OFR). He was a Director of Midas Merchant Bank and is Chairman of Ecobank Nigeria Plc, Midas Stockbrokers Limited, Clina-Immunoassay Laboratories and a Director of Total Health Trust Ltd among others. He was the Chairman of the Human Capital Policy Commission of the Nigerian Economic Summit Group.

He became the first African Master of the American College of Physicians in 2005. He was made Honorary Life President, Nigerian Society of Endocrinology in 2007 and is Life Patron of the Diabetes Association of Nigeria.

The immediate past President, King's College Old Boys Association, he is currently the Chairman, Board of Management, University College Hospital, Ibadan, and the Board of Trustees, Otunba Tunwase National Paediatric Centre, Ijebu-Ode.

A highly cited individual in bibliographies all over the world, including Who is Who in the World, he holds several traditional titles, including the hereditary Olor'ogun of Ijebu-Ode.

He is the founder of The Sonny Kuku Foundation.