Institution: University of Liverpool

Unit of Assessment: 10 – Mathematical Sciences

Title of case study: Informing clinical policy on epilepsy treatment

1. Summary of the impact (indicative maximum 100 words)

A team at the University of Liverpool has undertaken research that has informed practice and policy worldwide in the management of patients presenting with newly diagnosed epilepsy, which has achieved international impact on health. Seizures are common and 3-5% of the population will be given a diagnosis of epilepsy during their lifetime. Decisions about when to start treatment, and if so with which drug are crucial and can have a significant effect on outcomes for the individual and have significant economic consequences for society. The research includes the undertaking and analysis of data from randomised controlled trials. The data analysis is based on the statistical research initiated by Dr Paula Williamson while in the Department of Mathematical Sciences at the University of Liverpool between 1996 and 2000. The research identified the most appropriate first line treatments for patients with newly diagnosed epilepsy, addressing both clinical and cost effectiveness. This work has underpinned national policy and triggered the most recent update of the NICE (National Institute for Clinical Excellence) epilepsy guidelines in 2012.

2. Underpinning research (indicative maximum 500 words)

The HTA (Health Technology Assessment) funded study of Standard and New Antiepileptic Drugs (SANAD) compared standard and new antiepileptic drugs for patients with newly diagnosed epilepsy and compared clinical and cost effectiveness. The grant application for SANAD was submitted in 1998 and recruitment for the trials started in 1999. The underpinning research included the meta-analysis of randomised controlled trials and statistical method development. The rationale and framework for individual patient data meta-analysis of anti-epileptic drug trials was described, developed and implemented by Paula Williamson while a staff member in the Department of Mathematical Sciences at the University of Liverpool (between 1996 and 2000)[3.1,3.2,3.3,3.4] (references listed in Sect. 3), and continued when she joined the Department of Biostatistics in 2000. This work included advice on the selection of, and data management for, patient outcomes as well as the optimal statistical methods for data analysis.

The research outcomes of the SANAD trial provide the best evidence worldwide to inform treatment decisions. The trial identified lamotrigine (a new drug) as a first line treatment for newly diagnosed focal epilepsy as it was as effective as the standard treatment (carbamazepine) but better tolerated, and was cost effective[3.3,3.5]. Valproate (the standard treatment) was identified as the most effective treatment for patients with generalised epilepsy [3.4,3.6]. The analysis of SANAD[3.5,3.6] exploited the statistical methods developed by Williamson to assess competing risks of anti-epileptic drug failure, namely drug withdrawal due to inadequate seizure control or unacceptable adverse effects. Williamson proposed and applied a competing risks failure time model, assuming cause-specific proportional hazards, appropriate to this setting. Subsequent work demonstrated that in this particular setting, if such competing risks are ignored, there is an unacceptably high likelihood that important differential effects of the newer anti-epileptic drugs would be missed. In subsequent work, prognostic modelling of these data identified the characteristics of patients with differing seizure outcomes. This allows a stratified approach to patient counselling and treatment decisions.

The design of SANAD (e.g. sample size and outcomes) was informed by individual patient data meta-analysis (IPDMA) undertaken by Williamson and her group in the Department of Mathematical Sciences (which included H.E.Wilson (now Clough), C. Tudur (now Tudur-Smith) and C. Gamble)[3.1,3.2,3.3 and 3.4]. The parameter estimates for the sample size calculation for SANAD were taken from the results of a pivotal IPDMA [3.4]. The choice of outcomes was informed by the definitions proposed and applied by Williamson [3.1]. Subsequently data from SANAD were included in an updated meta-analysis. The SANAD project involved a team of 12 co-

investigators (including Prof Williamson) led by Prof AG Marson of the Department of Molecular and Clinical Pharmacology as PI. Other key members of the team were Profs G Baker and A Jacoby.

2. References to the research (indicative maximum of six references)

[3.1] Williamson PR, Marson AG, Tudur C, Hutton JL and Chadwick D. (2000) Individual patient data meta-analysis of randomised anti-epileptic drug monotherapy trials. Journal of Evaluation in Clinical Practice, 6(2): 207-214, DOI: **10.1046/j.1365-2753.2000.00236.x**

[3.2] Williamson PR, Clough HE, Hutton JL, Marson AG and Chadwick DW. (2002) Statistical issues in the assessment of the evidence for an interaction between factors in epilepsy trials. Statistics in Medicine, 21: 2613-2622, DOI: **10.1002/sim.1044**

[3.3] Preston CL, Marson AG, Williamson PR. Lamotrigine versus carbamazepine monotherapy for epilepsy. The Cochrane Database of Systematic Reviews 2002, Issue 4. Art. No.: CD001031. DOI: 10.1002/14651858.CD001031.

[3.4] Marson AG, Williamson PR, Wilson H, Hutton JL, Chadwick DW, on behalf of the epilepsy monotherapy group. Carbamazepine versus valproate monotherapy for epilepsy: A meta-analysis. Epilepsia 2002;43(5):505-513, DOI: **10.1046/j.1528-1157.2002.20801.x**.

[3.5] Marson AG, Al-Kharusi AM, Alwaidh M, Appleton R, Baker GA, Chadwick DW, Cramp C, Cockerell OC, Cooper PN, Doughty J, Eaton B , Gamble C, Goulding PJ, Howell SJL, Hughes A, Jackson M, Jacoby A, Kellett M, Lawson GR, Leach JP, Nicolaides P, Roberts R, Shackley P, Shen J, Smith DF, Smith PEM, Tudur Smith C, Vanoli A, Williamson PR on behalf of the SANAD Study group. Carbamazepine, gabapentin, lamotrigine, oxcarbazepine or topiramate for partial epilepsy: results from the SANAD trial. Lancet 2007;369:1000-1015, DOI: **10.1016/S0140-6736(07)60460-7**.

[3.6] Marson AG, Al-Kharusi AM, Alwaidh M, Appleton R, Baker GA, Chadwick DW, Cramp C, Cockerell OC, Cooper PN, Doughty J, Eaton B , Gamble C, Goulding PJ, Howell SJL, Hughes A, Jackson M, Jacoby A, Kellett M, Lawson GR, Leach JP, Nicolaides P, Roberts R, Shackley P, Shen J, Smith DF, Smith PEM, Tudur Smith C, Vanoli A, Williamson PR on behalf of the SANAD Study group. Valproate, lamotrigine or topiramate for generalized and unclassifiable epilepsy: results from the SANAD trial. Lancet 2007;369:1016-1026, DOI: **10.1016/S0140-6736(07)60461-9**.

These publications describe the research undertaken by Prof Williamson while a member of the Department of Mathematical Sciences; the Lancet publications represent reports on the SANAD trial in its entirety.. Many of the publications listed above, where the research carried out in the Department of Mathematical Sciences is described, are highly cited, with Refs [3.1], [3.4-6] accruing 28, 52, 229 and 218 citations respectively by September 2013 (according to the Web of Knowledge). The publications appear in high-impact journals; Statistics in Medicine is rated A* in the ARC list of journals. The Lancet has an Article Influence score of 13.6, ranked 2 out of 153 medical journals; the Journal of Evaluation in Clinical Practice has an Article Influence score of 0.468, ranked 55 out of 153 medical journals; and Epilepsia has an Article Influence score of 1.2, ranked 30 out of 191 journals of clinical neurology.

4. Details of the impact (indicative maximum 750 words)

It is crucially important for public policy to identify clinical treatments which combine cost-effectiveness with clinical efficacy and minimal adverse effects, and this requires an ongoing process of evaluation of new pharmaceutical products as they become available. This evaluation requires large scale clinical trials of the kind described above. The research described here has made a significant impact in this regard at both the national and international level.

Firstly, the SANAD trial was the driver for a major update in 2012 of the clinical guidelines for the treatment of epilepsy published by NICE (the National Institute for Clinical Excellence). NICE is the main source of guidance on treatment for healthcare professionals in the UK. In 2008 it commissioned the National Clinical Guidelines Centre for Acute and Chronic Conditions (NCGCACC) to partially update the 2004 NICE guidelines on epilepsy treatment, NICE Clinical Guideline 20 (2004). The first stage in the update was the publication in 2009 of a "Scope" document [5.1] (references listed in Sect 5) which defined the remit for the guideline update. Section 3 of this document (3.2 section d), headed "Clinical need for the guideline", stated **"However, a recent large multicentre trial (the SANAD trial) evaluating newer drugs in newly diagnosed epilepsy (accepting some limitations) suggested that sodium valproate should be the drug of choice in generalised and unclassifiable epilepsies, and lamotrigine in partial epilepsies. We therefore consider it necessary to review new evidence regarding anti-epileptic drugs within an update of the NICE clinical guideline,"** This demonstrates that the SANAD research was the most significant trigger for the update.

Moreover it is clear from the draft consultation version of the guidelines [5.2] published in 2010 that the SANAD researchers were asked by NCGCACC to supply additional unpublished research. The final updated version of the guidelines was published in 2012 as NICE Clinical Guideline 137 (2012) [5.3]. The Introduction to these guidelines repeats the quotation above, confirming that SANAD was the major motivation for the update; this introduction appears as p7 of the full PDF document and as the "Abstract" on the webpage for the updated guideline. It is clear from Sect. 1.9 of the guideline, especially 1.9.4, 1.9.12 and 1.9.14, that the treatment recommendations have been modified in 2012 to place a greater emphasis on sodium valproate and lamotrigine, in line with the SANAD findings.

Secondly, the International League Against Epilepsy (ILAE) Guidelines cited SANAD in 2009 [4] as an important influence on work on updating their guidelines for monotherapy (i.e. the treatment by a single drug). The updated guidelines were finally published in 2013 [5.5]. The ILAE is the major international professional organisation representing all those interested in the field of epilepsy. The **ILAE** publishes an official journal, *Epilepsia*, which is the leading, most authoritative source for current clinical and research results on all aspects of epilepsy. *Epilepsia* periodically publishes the ILAE Guidelines which represent the current international standard on epilepsy treatment. Ref.[5.4] above was also published in this journal.

Finally German Epilepsy guidelines published in 2008 [5.6] cite SANAD underpinning the recommendation for lamotrigine as first line treatment.

Beneficiaries of this work include

- People with epilepsy, through better informed treatment choices.
- The NHS and other health systems caring for people with epilepsy, through providing effective and cost effective care.
- Guideline developers including NICE, which have used these data to underpin their guidance.

Naturally it will be some time before impacts on public health resulting from such recent changes in the guidelines can be measured.

5. Sources to corroborate the impact (indicative maximum of 10 references)

NICE Guidelines

[5.1] National Institute for Health and Clinical Excellence (NICE) Scope document. Section 3.2 (d) references the SANAD trial as a major driver for update of the guidance.

[5.2] Draft consultation version of the NICE guidelines (2010). SANAD researchers were asked by NCGCACC to supply additional unpublished research (Page 60, Line 23) to inform the guidance updates.

[5.3] NICE Clinical Guideline 137 published 2012; see The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care at

International League Against Epilepsy (ILAE) guidelines:
[5.4] See p66 of http://www.ilae.org/Visitors/Documents/ILAEAnnual-Report2009_000.pdf showing inclusion of SANAD data in updated guidance.

[5.5] Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes (Epilepsia 2013), further references role of SANAD trial on International guidance.

German guidelines
[5.6] Leitlinien für Diagnostik und Therapie im der Neurologie. Stuttgart: Georg Thieme Verlag, 2008. Document link is original German guidance, but SANAD trial is referenced on page 11 and the base of page 21 references SANAD data