Impact case study template (REF3b)

Title of case study: Novel Omega 3 fatty acid therapy for sickle cell disease

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

This case study outlines the impact of novel omega-3 fatty acid therapy for sickle cell disease on health and policy. 128 patients on the treatment since 2010, and another 300 who started to receive it in June 2012 have seen remarkable improvements in health and quality of life as assessed by reductions in hospital admission and absence from work/school due to the disease. A panel of experts set up by the Ministry of Health of Sudan to evaluate the evidence recommended the integration of the therapy in the management of the disease in a policy report dated December 20, 2012. The Ministry has accepted the recommendation.

2. Underpinning research (indicative maximum 500 words)

Background **–** Sickle Cell Disease (SCD) is the most common hereditary blood disorder which results from beta globin gene mutation. Vaso-occlusive crisis is the main cause of multi-organ damage, disability (physical and mental) and death. In Sub-Sahara Africa, a region with highest prevalence of the disease, life expectancy is less than 30 years and more than 230,000 babies are born with sickle anaemia every year. The corresponding annual birth in the UK is about 300 and the estimated number of sickle cell sufferers is 25,000.

Vaso-occlusive crisis in SCD was thought to be due to mechanical obstruction of blood vessels by rigidly distorted (sickled) red blood cells. However, it is now accepted that the propensity of their blood cells to adhere to vascular endothelium and inflammation are the predisposing factors. The aforementioned factors are modulated by cell membrane fatty acid composition. Studies conducted by our group (Ren et al 2005a & b, 2006) and others have found that SCD patients have an abnormal blood cell (red cell, platelet and mono-nuclear) fatty acid composition. The abnormality, which cannot be explained by an insufficient intake, is characterised by low levels of the vital omega 3 fatty acids, eicosapentaenoic (EPA) and docosahexaenoic (DHA). This finding led us to hypothesise, "*Supplementation with EPA and DHA will reduce vas-occlusive painful crisis and hospitalisation*". To test the postulation, a double-blind, placebo-controlled, randomisd clinical trial was conducted between January 2009 and March 2010. Trial registration number ISRCTN80844630.

Patients and method **-** 140 Sudanese homozygous (HbSS) sickle patients recruited from Khartoum Teaching Hospital (Sudan) were allocated based on computer-generated randomisation sequence. The patients, caregivers, staff of Sickle Cell Referral Clinic and researchers were blinded. The patients received omega 3 (n=70) or placebo (n=70) capsules daily for one year. Primary endpoint was annualised rates of clinical vaso-occlusive crisis; secondary end points: haemolytic crisis, rate of blood transfusion, school attendance, haemoglobin level and mean cell volume. Data were collected through monthly clinical follow-up. Of the 140 randomised patients, 128 completed the study.

Ethical issue - The study was approved by the Ethics Committee of the Faculty of Medicine, University of Khartoum, Sudan and the Research Ethics Committee of Southampton & South West Hampshire, UK (REC reference number-05/Q1702/48).

Findings which to led to the impact **-** Omega 3 treatment reduced significantly clinical vaso-occlusive events and related hospitalisation, incidence of haemolytic crisis, blood transfusion rate, and school absence per year-days. Moreover, there was no incidence of overt stroke in the treated patients.

Interpretation which led to the impact **-** Omega 3 fatty acids are effective therapy for prevention of vaso-occlusive and haemolytic crises for homozygous SCD. It is safe and affordable treatment particularly for patients from sub-Saharan who have limited access to the conventional therapies (blood transfusion and hydroxyurea) and regular clinical and laboratory monitoring (Daak et al 2013).

The study was conducted by researchers from London Metropolitan University led by

Professor Kebreab Ghebremeskel in collaborations with the University of Khartoum and Efamol Ltd. (UK).

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

- Daak A, Ghebremeskel K, Hussan Z, Attallah B, Elzan H, Crawford M, and El Bashir M (2013) Effect of omega 3 fatty acid supplementation on patients with sickle cell anaemia: randomised, double-blind, placebo-controlled trail. *American Journal of Clinical Nutrition 97(1):37-44. Impact factor 6.7*
- Ren H, Ghebremeskel K, Okpala I, Ugochukwu C, Crawford M and Ibegbulam (2006) Abnormalities of red cell membrane fatty acids in sickle cell haemoglobin C (HbSC) disease is not as remarkable as in sickle cell anaemia (HbSS). *Prostaglandins, Leukotrienes and Essential Fatty Acids 7 (1):1-6. Impact factor 3.23*
- Ren H, Ibegbulam O, Okpala I, Ghebremeskel K, Ugochukwu C and Crawford MA (2005a) Steady state haemoglobin level in sickle cell anaemia increases with an increase in the proportion of erythrocyte membrane n-3 fatty acids. *Prostaglandins, Leukotrienes and Essential Fatty Acids 72(6):415-421. Impact factor 3.23*
- Ren H, Okpala I, Ghebremeskel K, Ugochukwu C, Ibegbulam O, Crawford MA (2005b) Blood mononuclear cells and platelets have abnormal fatty acid composition in homozygous sickle cell disease. *Annals of Hematology 84(9):578-583. Impact factor 2.62*

Research Grants

- **Awardee:** Ghebremeskel K; *Title* - Lipidomics in Human Development, Health and Chronic Diseases; *Sponsor* - EU 6th Framework Programme, Marie Curie Transfer of Knowledge (Contract no. MTKD-CT-2005-029914); *Grant period*- March 01, 2006 – February 28, 2010; *Amount-:* 1,285,600 Euro
- **Awardee:** Ghebremeskel K; *Title***-** Omega 3 Fatty Acids for prevention of vaso-occlusive crisis in patients with sickle cell disease; *Sponsor* - Efamol Limited (UK); *Grant period*- January 2009 – June 2012; *Amount-:* £15,000 and 500,000 omega 3 capsules (retail price £167,000 at £20/60 capsules).
- **Awardee:** Daak A (PhD stipend); *Title***-** Omega 3 Fatty Acids for prevention of vaso-occlusive crisis in patients with sickle cell disease; Sponsor - The Kitchener School of Medicine Trust Fund; *Grant period*- July 2008 – March 2012; *Amount*- £35,200.
- **Awardee:** Ghebremeskel K; *Title*- Fatty acid status of patients with sickle cell anaemia; *Sponsor*- Sir Halley Stewart Trust; *Amount-:* £38,615; *Grant period*- 1999-2002.
- **Awardee:** Ren H (PhD Fellowship); *Title*- Sickle cell disease and membrane lipid disorder; **Sponsor:** American Oil Chemists' Society Thomas H Smouse Memorial Graduate Fellowship; *Amount*- $45,000, *Grant Period*- 2004-2006.

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

The need for new therapy

The current treatment options for patients with sickle cell disease are blood transfusion, anticoagulant, antiplatelet and thrombolytic agents, and hydroxyurea. High-risk patients, particularly children are treated with periodic blood transfusion. This therapy reduces recurrent and initial stroke by over 80%. Unfortunately, it is associated with a high rate of complications – transmission of infective agents, allo-immunisation, transfusion reactions, and iron overload. Anticoagulant, antiplatelet and thrombolytic agents have been used for the prevention of stroke in children However, the efficacy of these drugs has not been fully investigated in randomised controlled trials and there is concern about their safety. Hydroxyurea is prescribed for patients with moderate-to-severe sickle cell disease. The long-term cellular

and molecular adverse effects of hydroxyurea, a cytotoxic drug originally developed for cancer treatment, on patients are unknown. Hence, safe, affordable and effective omega 3 fatty acid based therapy was developed to help prevent vaso-occlusive crisis and its manifestation particularly for sickle cell patients in sub-Sahara Africa.

Current beneficiaries and health impact

128 homozygous sickle cell patients have been on the treatment since 2010 and another 300 started to receive it in June 2012. The impact of the therapy on health and quality of life of the patients has been remarkable. This is manifested in significant reductions in frequency and severity of vaso-occlusive (painful) episodes and haemolytic (severe anaemia) crises, blood transfusion rate, number of hospitalisation and absence from work/school due to sickle cell related illness in the 428 patients. Moreover, there has not been any incidence of stroke in the patients on the therapy, although it is a common occurrence in homozygous sickle cell patients in the clinic particularly in children.

Impact on policy

As the result of the compelling evidence of the efficacy of the therapy and demand for the medication by ever-increasing number of patients in Khartoum and elsewhere in Sudan, the Federal Ministry of Health set up a panel of experts consisting of researchers, clinicians, community health professionals and members of parliament to evaluate the evidence. On the 20th of December 2013, the panel published evidence-based policy report which recommends the integration of the therapy in the management package of sickle cell disease in the country. The Ministry has accepted the recommendation.

Impact on business

Efamol Limited, the UK company which formulated the tailored omega 3 therapy, so far, has supplied for the patients 500,000 capsules free of charge. At present, the company is discussing with the Ministry of Health to market the therapy in the country at cost price.

Collaborators

- Faculty of Medicine, University of Khartoum – Professor Mustafa El-Bashir MD, PhD (*Clinical Coordinator*), Professor Bakhita Attallah MD, and Drs Haj Azan MD and Zahir Hassan MD (*Sickle Cell Referral Clinic*) and Dr Ahmed Daak MD PhD (*Researcher, our former PhD student who worked on the project*).
- Efamol Limited UK (Mr Peter Clough) - Provided tailored omega 3 fatty acid formulation for the patients. To date, the company has supplied 500,000 omega 3 capsules (retail price £167,000 at £20/60 capsules).

Dissemination

- *Peer Reviewed Publication* - American Journal of clinical Nutrition (2013) 97(1):37-44.
- *Conference presentation* - 9th Congress of the international Society for the study of Fatty Acids and Lipids *Maastricht, The Netherlands, May 29 – June 2, 2010 (Oral presentation)*
- *Conference presentation* - 10th Congress of the international Society for the study of Fatty Acids and Lipids Vancouver, Canada, *May 26 – 30, 2012 (Oral presentation).*
- *Mass Media* - National Television of the Republic of Sudan(December 29, 2012), Al-Ray Alaam and Alsudani News Papers (December 30, 2012)
- *Mass Media Website* - Al- Ray Alaam Report. http://www.alray-aam.net/index.php/alray-aam-hot-news/rayaam-new-topics/rayaam-sudanese-affairs/12376-2012-12-29-21-49-04.
- *Invited Lecture* - "Omega 3 therapy for sickle cell disease" at the College of Medicine and Health Sciences, Sultan Qaboos University (March 19, 2012).
- *University- Wide Faculty Seminar* – Invited visiting clinicians, scientists and academic

staff at the Faculty of Medicine, University of Khartoum (26 December 2012)

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

1. *Patients' Testimony* - Sickle cell patients who are benefiting from the therapy
2. *Medical Staff Testimony* - Medical staff of Sickle Cell Referral Clinic, Ibn-Aoaf Paediatrics and Khartoum Teaching Hospitals, Khartoum (Sudan).
3. *Company Testimony* – Mr Peter Clough, the Research Coordinator of Efamol Limited (UK) the company which provided the omega 3 capsules and financial support for the study.
4. *Ministry of Health Report* - A policy report by an expert panel set up by the Federal Ministry of Health of Sudan at the behest of the sickle cell patients and medical staff of Ibn-Aoaf Sickle Cell Clinic and Khartoum Teaching Hospital. (An evidence based policy report, 20 December 2013).
5. *American Journal of Clinical Nutrition (Highlights of recent research)* http://ajcn.nutrition.org/site/misc/release2.xhtml
6. *DHA.EPA Omega 3 Institute* - http://www.dhaomega3.org/Other-Health-Conditions/DHAEPA-Omega-3-Suggested-as-Therapy-for-Sickle-Cell-Anemia

A comment from an independent research in the field about the study and publication which underpinned the impact, it reads, "This present study and publication is one of the most promising and exciting in recently- published research to appear in the DHA/EPA omega-3 field with respect to the complementary treatment of a most serious clinical condition".

7. *Reuters Health* - http://www.modernmedicine.com/news/omega-3s-benefit-sickle-cell-patients-single-center-study. An article in Reuters Health, the premier supplier of health and medical news on the Internet, about the study and publication which underpinned the impact.