Institution: De Montfort University

Unit of Assessment: 3

Title of case study: A Single-Drop Blood Test to Identify Patient Nonadherence to Cardiovascular Medication, Change Care Delivery and Optimise Treatment Plans

Period when the underpinning research was undertaken: 2007–2019

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Prof. Sangeeta Tanna	Professor of Pharmaceutical Analysis	1 September 2000–present
Dr Graham Lawson	Principal Lecturer	October 1983 to July 2011
	Honorary SRF	August 2011 to April 2018

Period when the claimed impact occurred: July 2016–31 December 2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

Research at DMU's Leicester School of Pharmacy has developed the first non-invasive, single-drop blood test for assessing nonadherence to prescribed cardiovascular medicines. This has been used in clinical practice by hospitals in Kenya and Iraq, resulting in the following impacts:

- Improved healthcare plans and optimised treatment for heart disease patients who were found not to be adhering to their prescribed medication.
- Improved clinical outcomes through better control of blood pressure, resulting in reductions in emergency hospital admissions and significantly lowered risks of cardiovascular events.
- Enhanced adherence to prescribed medicines through positive changes in patients' behaviour.
- Changes to clinical practice by embedding pharmacists and hospital social workers within the clinical teams that plan and deliver patient care.
- Identification of the high risk of poor-quality or counterfeit drugs circulating within the Kenyan healthcare system, prompting a submission to an ongoing national-level review of medicines safety.

2. Underpinning research

Cardiovascular disease (CVD) affects more than 1,000,000,000 people worldwide. Effective management and treatment of these patients requires strict compliance with a medication regime that comprises a combination of multiple cardiovascular medicines. Most patients, however, struggle to comply, partly because of the number and combination of drugs they need to take on a daily basis. The World Health Organization reports that up to 50% of all prescribed CVD medicines are not taken as intended, resulting in poor patient outcomes and excess healthcare costs. Monitoring patients' adherence to their treatment plan is therefore critical.

From 2007 to 2011, National Institute for Health Research (NIHR)-funded research at DMU, led by Professor Sangeeta Tanna and supported by the late Dr Graham Lawson, developed and validated a minimally invasive blood test using the analysis of a single drop of blood (~20µl) to determine the concentration of drugs in blood for much needed pharmacokinetic studies in newborn babies. Historically, pharmacokinetic studies were not conducted in the paediatric population due to the repeated large volumes of blood required using conventional sampling (~5–10ml). Without this data, optimal drug dosing regimens remain unknown and risk of adverse side effects is heightened.

A pioneering methodology developed by Tanna and Lawson, in collaboration with University Hospitals of Leicester NHS Trust, overcame this hurdle by using liquid chromatography-mass spectrometric analysis of dried blood spots (DBS) from a single pinprick. Tanna validated this

method by first determining the quantity of the therapeutic drug dexamethasone, used for the treatment and prevention of chronic lung disease in newborns, in microvolume DBS samples collected from premature neonates [R1]. She then demonstrated its efficacy at quantifying concentrations of captopril, an angiotensin-converting enzyme inhibitor widely used in paediatric cardiology to treat congestive heart failure [R2].

From 2012 the research using DBS analysis was expanded into clinical care and management of adults with CVD. Using DBS sampling and analysis, Tanna was able to identify, unequivocally, the extent of patients' adherence to prescribed cardiovascular drugs. This represented another novel breakthrough as there is currently no 'gold standard' method for assessing medication adherence in routine clinical practice. This work was successfully piloted with 41 people (volunteers) in a study funded by DMU's Gunn and Carter Fellowship (GBP26,000) and a DMU research student bursary. It showed that the level of nonadherence to prescribed CVD drugs was 27% [R3, R5]. Proof of concept of the simple blood test was achieved. Crucially, the novel methodology permitted blood samples to be self-collected by the patient and posted to DMU's laboratory for analysis, reducing the burden on health practitioners and services [R4].

Following its validation, the test was used to assess adherence to prescribed drug therapy among hospital patients in Iraq (2016–2019); 303 patients who had been prescribed CVD medicines were recruited from the Al Sader Teaching Hospital and Misan Cardiac Centre [R6]. It was funded by an Iraq Ministry of Health PhD studentship (GBP58,000). Data derived from DBS analysis showed that 49% of patients were nonadherent to one or more of their prescribed medications. This was an important finding as it explained why this group of patients had a poor prognosis; lack of adequate control of their high blood pressure had significantly increased the risk of other cardiovascular events.

Under a DMU Global Challenges Research Fund (GCRF) grant (GBP28,000), studies were initiated in Kenya where 287 patients were recruited from the main public hospital – Kenyatta National Hospital (KNH) – and a leading private hospital – Aga Khan University Hospital (AKUH). Between July 2019 and March 2020, DBS samples were collected locally following training of hospital staff by Tanna and were analysed at DMU. The results showed that 51% of patients at KNH and 31% of patients at AKUH were nonadherent to their heart disease medication. An extension of the studies within Kenya has been hampered by Covid-19, limiting further data gathering and/or implementation of changes to hospital policies and processes. The two studies in Iraq and Kenya, however, marked the first time that this type of patient microsample was collected in either country.

3. References to the research

[R1] Patel, P., Tanna, S., Mulla, H., Kairamkonda, V., Pandya, H. and Lawson, G. (2010) 'Dexamethasone quantification in dried blood spot samples using LC-MS: the potential for application to neonatal pharmacokinetic studies', *Journal of Chromatography B*, 878(31): 3277–3282; https://doi.org/10.1016/j.jchromb.2010.10.009

[R2] Lawson, G., Mulla, H. and Tanna, S. (2011) 'Captopril determination in dried blood spot samples with LC-MS and LC-HRMS: a potential method for neonate pharmacokinetic studies', *Journal of Bioanalysis and Biomedicine*, 4(2): 16–25; http://doi.org/10.4172/1948-593X.1000058

[R3] Lawson, G., Cocks, E. and Tanna, S. (2013) 'Bisoprolol, Ramipril and Simvastatin determination in dried blood spot samples using LC-HRMS for assessing medication adherence', *Journal of Pharmaceutical and Biomedical Analysis*, 81/82: 99–107; http://doi.org/10.1016/j.jpba.2013.04.002

[R4] Tanna, S. and Lawson, G. (2016) *Analytical Chemistry for Assessing Medication Adherence*, Amsterdam: Elsevier; ISBN 9780128054635

[R5] Bernieh, D., Lawson, G. and Tanna, S. (2017) 'Quantitative LC-HRMS determination of selected cardiovascular drugs, in dried blood spots, as an indicator of adherence to

medication', *Journal of Pharmaceutical and Biomedical Analysis*, 142: 232–243; http://doi.org/10.1016/j.jpba.2017.04.045

[R6] Alalaqi, A., Lawson, G., Obaid, Y. and Tanna, S. (2019) 'Non-adherence to cardiovascular pharmacotherapy in Iraq assessed using 8-items Morisky questionnaire and analysis of dried blood spot samples', *British Journal of Pharmacy*, 4(1); http://doi.org/10.5920/bjpharm.627

AWARDS/RECOGNITION

Tanna and Lawson were awarded the Royal Society of Chemistry Analytical Methods Prize in 2010 for their methodology of liquid chromatography-mass spectrometric analysis of DBS. The research was a finalist in *Times Higher Education*'s Research Project of the Year in 2012.

4. Details of the impact

From 2016, DMU's research-based methodology to objectively assess nonadherence to medications progressed from the laboratory to clinical application in hospitals in Iraq and Kenya. In doing so, it optimised treatment plans for patients with cardiovascular disease and improved clinical outcomes; led to changes in clinical practice to improve medication adherence; and raised the alarm for the circulation of poor-quality or counterfeit drugs within the Kenyan health system [C1-C4].

(1) OPTIMISING PATIENT TREATMENT PLANS AND IMPROVING CLINICAL OUTCOMES

The Al Sader Teaching Hospital and Misan Cardiac Centre in Iraq were the first in the world to implement DMU's DBS microsampling test in a clinical environment, targeting patients with heart disease. Iraq is widely recognised as experiencing a high burden of cardiovascular disease relative to global averages. A 2018 article in *International Journal of Public Health* (https://doi.org/10.1007/s00038-017-1012-3) demonstrated that the age-standardised, disability-adjusted life years rates in the Eastern Mediterranean Region are considerably higher than the global average, while Iraq has the second highest CVD death rate in this 22-country region.

In 2019 Tanna trained healthcare professionals in Kenya in collecting, storing, transporting and preparing DBS samples for analysis at DMU. She hosted workshops to facilitate knowledge transfer with partners from both hospitals in Kenya. Use of the DMU blood test in Kenya was seen, in part, as a way to identify whether non-adherence to CVD drugs might be attributed to the sale of poor quality, unregistered or counterfeit medications to patients [C4]. According to the WHO (https://apps.who.int/iris/bitstream/handle/10665/326708/9789241513425-eng.pdf?ua=1), 42% of all fake medicines reported to them between 2013 and 2017 were from Africa.

Analysis of close to 600 patient DBS samples from both countries provided the first clear evidence to clinicians in Iraq and Kenya of the extent of medication nonadherence among patients with heart disease [C1–C4]. The findings on blood drug levels for each individual patient revealed that 285 patients (148 in Iraq and 137 in Kenya) were nonadherent to one or more of their prescribed cardiovascular drugs. Through discussions with patients to establish possible reasons for nonadherence, clinicians were able to make informed decisions about changes to medication and to develop more personalised patient treatment plans, for example decreasing the complexity of prescribed dosing regimens [C2, C4].

This is a significant improvement on previous practice where the approach was simply to increase the dose or add another medicine to the prescription for patients with poor symptom control [C2, C4]. At KNH, where the highest percentage (51%; n = 122) of heart disease patients were found to be nonadherent to prescribed drugs, the lead clinical pharmacist said subsequent changes to treatment plans had 'decreased the risks of cardiovascular events' for patients, 'impacting positively on patient's social economic standing due to adherence to medication' [C4]. He said 'medical doctors greatly benefitted' from DMU's research as it provided them with the evidence base to change the healthcare plans of these patients. This resulted in 'decreased emergency hospital visits due to spiking blood pressure' and a 'better quality of life for the patient' [C4]. Clinicians reported positive changes in patient behaviour in terms of taking their medications as prescribed, resulting in enhanced compliance [C2, C4]. The lead cardiologist at Misan Cardiac Centre in Iraq said: 'As the data were specific for each patient and for each

medication in the collected Iraqi sample, I reacted to each case of non-adherence individually and started checking the treatment plan with consideration of patient perspective' [C2].

(2) CHANGING CLINICAL PRACTICE TO IMPROVE LONG-TERM MEDICATION ADHERENCE

The research findings led KNH to change its clinical practice by formally embedding pharmacists, nurses and hospital-based social workers within the clinical teams [C4]. Pharmacists now play a pivotal role in carrying out regular medication therapy management and in educating patients on the importance of adhering to prescribed drug therapy [C4]. Nurses educate patients on the need to frequently monitor blood pressure and social workers are now used to provide counselling and direct patients as to where they should go to obtain their medication [C4]. There have been fundamental changes to KNH patient treatment plans, including reductions to patients' pill burden and a decrease in polypharmacy, which boosts adherence and reduces costs [C4]. The packaging of medicine has also been improved to enable the elderly to take their medicine correctly without confusion [C4].

At Misan Cardiac Centre, the role of clinical pharmacists in the medical team has been strengthened; they now communicate with patients on the importance of adhering to prescribed drug therapy [C2]. The Centre recognised the wider applicability of the DMU test in the assessment of medication adherence for other chronic diseases in Iraq such as diabetes [C2].

(3) IDENTIFYING HIGH RISK OF SUBSTANDARD OR COUNTERFEIT MEDICINES IN THE KENYAN HEALTH SYSTEM

DMU's research findings raised a critical healthcare issue: further evidence of the high risk of poor-quality or counterfeit drugs circulating within the Kenyan healthcare system and unknowingly being made available to patients [C3, C4]. This came to light because DMU's research findings revealed that 117 (49%) of the KNH patients, who appeared non-compliant based on the DMU analysis, had in fact taken their medication. However, the drugs could not be detected in their DBS samples. This was seen as an alarming finding and confirmed suspicions raised by clinicians over the poor quality of particular drugs that were being supplied [C4].

The consultant clinical pathologist at AKUH concluded: 'The absence of detectable levels of these drugs in patients who reported that they were compliant is concerning given that one of the possible explanations could be substandard medication' [C3]. The clinical pharmacist at KNH wrote [C4]: 'The DMU results have now highlighted the possible existence of such poor-quality medications in circulation within the health care system in Kenya and confirms suspicions raised by some clinicians on the poor quality of particular drugs supplied. Clinicians have previously noted that different brands of drugs elicit different responses.'

The DMU results revealed that different brands of prescribed cardiovascular medicines gave different results with respect to blood drug levels. As of the end of the impact period, suspected brands were under investigation; the research findings have informed the choice and brand of cardiovascular medication stocked in the KNH pharmacy department [C4]. KNH's clinical pharmacist reported in December 2020 that the matter had been taken up by the national regulatory body. He wrote:

> The matter of poor quality, unregistered drugs in circulation is now being reviewed by the Pharmacy and Poisons Board within the Ministry of Health in Kenya that oversees medicines safety. This is with a view to adopting further policies to address bad practices and the sale of poor-quality, unregistered or counterfeits medication. This will be monitored by the pharmacovigilance authority that follows up on complaints due to medicines and submits their reports to the regulator. [C4]

5. Sources to corroborate the impact

[C1] Statement from the Director General, Misan Health Directorate, Iraq to corroborate the impact on regional health services.

[C2] Statement from the Dean of the College of Medicine, University of Misan, Iraq to corroborate the impact on clinical practice and patients at Misan Cardiac Centre.

[C3]	Statement from Assistant Professor and Consultant Clinical Pathologist at Aga Khan University, Nairobi, Kenya to corroborate the impact on clinical practice and patients at Aga Khan University Hospital.
[C4]	Statement from Clinical Pharmacist at Kenyatta National Hospital, Nairobi, Kenya to corroborate the impact on clinical practice and patients at Kenyatta National Hospital.