Institution: The University of Nottingham		
Unit of Assessment: UoA5		
Title of case study: Improving patient outcomes and treatment guidelines through the study of Hepatitis C		
Period when the underpinning research was undertaken: 1993-present		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): William Irving	**Role(s) (e.g. job title):** Professor of Virology	**Period(s) employed by submitting HEI:** 1990-present
Period when the claimed impact occurred: 2014-ongoing		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Pioneering research on the epidemiology of Hepatitis C Virus (HCV) by Professor Irving has resulted in health benefits to patients worldwide, improved national and international treatment guidelines and increased international uptake of direct-acting antiviral drugs. The foundation of HCV Research UK, a national clinical database and biobank resource, supported the NHS Early Access Programme (EAP) to provide antiviral drugs ahead of licensing. HCVRUK analysis of the positive outcomes of the EAP encouraged the NHS and other international health providers to adopt these new drugs to treat patients with life-threatening end stage liver disease, decreasing mortality and requirement for liver transplants associated with HCV infection. Professor Irving's study of the care pathway of HCV patients from diagnosis to cure, including HCV patients who inject drugs, in the HepCATT study prompted the NHS to introduce a national system for the monitoring of disease prevalence and informed national and international treatment guidelines. The implementation of these guidelines has improved patient outcomes and treatment cost for health care providers.

2. Underpinning research

The World Health Organisation (WHO) estimates that 71 million people globally had chronic HCV infection in 2020. In England alone, Public Health England (PHE) estimates 89,000 people were living with chronic HCV infection in 2020, of whom an estimated two thirds were undiagnosed. Chronic HCV can cause liver cirrhosis or liver cancer in a significant number of those infected. Three pioneering research initiatives by Professor Irving have delivered considerable insight into the epidemiology and treatment of HCV infection in the UK and internationally: i) HCV Research UK (HCVRUK); ii) the study of the cascade of care; and iii) the Hepatitis C Assessment through to Treatment Trial (HepCATT) study.

i HCVRUK: a research resource for the longitudinal study of HCV infection in the UK

In the early nineties when a test for HCV detection had just come out and little was known about the epidemiology, risk factors and clinical consequences of HCV infection, Professor Irving, funded by the Department of Health (1993-2011) **[7]**, GSK and Pfizer **[8, 9]**, coordinated the collection of detailed epidemiological data from 2500 HCV patients across the East Midlands, including Nottingham, Sheffield, Derby, Lincoln and Leicester **[1]**. This collection of data constituted the Trent Cohort, which became a local proof of concept of the potential of a national-scale cohort. With the support of the Medical Research Foundation **[10],** Professor Irving in collaboration with Professor John McLauchlan (University of Glasgow) co-founded HCVRUK in 2013.

HCVRUK (hcvresearchuk.org), is a national research infrastructure that aims to facilitate research into all aspects of HCV infection in the UK. It integrates a bespoke database of detailed longitudinal clinical data from 12,000 HCV-infected patients and a biobank resource of over 150,000 patient samples **[2]**. The HCVRUK consortium, co-chaired by Professors Irving and McLauchlan, includes clinicians from 59 NHS Trusts and Scottish Health Boards, scientists from UK academic centres and public health specialists from PHE and Health Protection Scotland**.** To December 2020, 91 applications have been granted for the use of data and/or biological samples in research studies, including by pharma industry and academia, both in the UK and abroad. Two major studies enabled by HCVRUK and with key involvement of Professor Irving have delivered substantial impact:

i.i Research on direct-acting antiviral (DAAs) drugs used in the NHS Early Access Programme (EAP). In 2014, Professors Irving and McLauchlan co-led the monitoring of the outcomes of the EAP commissioned by NHS England, wherein patients with advanced liver disease were provided access to the new DAAs ahead of licensing. HCVRUK provided the infrastructure to recruit patients and collect and share clinical data and samples. Professor Irving and collaborators were then able to provide the first published evidence of high cure rates from DAA therapy in this group of patients **[3]**.

i.ii STratified Medicine to OPtimise the treatment of HCV (STOP-HCV). Professor Irving and HCVRUK played an important role in securing GBP4,168,144 from the MRC **[11]** for the formation of STOP-HCV (stop-hcv.ox.ac.uk/about-stop-hcv), a consortium of eleven Universities and five pharma companies, led by Oxford University, that was underpinned by HCVRUK's clinical database and biosamples. Of the seven integrated work strands of STOP-HCV, Professor Irving co-led work strand 1 (provision of well-characterised HCVRUK patient samples and metadata) and work strand 5 (biomarkers). STOP-HCV has so far generated over 40 primary publications relating to the pathogenesis, natural history and optimal management of HCV infection **[4** as an example, with Professor Irving's authorship in at least 9 other publications since 2015**] [13, 14]**.

ii Research into HCV patients' cascade of care. The cascade of care is the pathway of a patient from diagnostic test, through care and treatment, to cure. Professor Irving, in collaboration with PHE, informed the design of an algorithm that allowed modelling of prevalence of HCV in England, as well as the proportion of HCV patients diagnosed and treated and the proportion of and reasons for patient drop-out **[5].** Additionally, Professor Irving's research into the cascade of care identified, quantified and validated interventions to improve case finding, referral, treatment uptake, retention in care and cost-effectiveness. An example of best practice intervention that emerged from Professor Irving's cascade of care studies is 'reflex testing', which sequentially tests a single blood sample both for anti-HCV antibodies and HCV RNA. Another example is the antiviral resistance testing, which tests the resistance of the virus to DAAs and informs the selection of optimal treatment.

iii HepCATT Study. Over 85% of diagnosed HCV patients in England acquired the infection as a collateral of injecting drugs. In order to significantly reduce overall disease incidence, it is important to study and design strategies that specifically target people who inject drugs (PWID). Prompted by earlier local-scale studies where Professor Irving witnessed large patient drop-out, he subsequently co-led the HepCATT study at a national scale (Department of Health funding **[12]**), which demonstrated the effectiveness of the introduction of health-care staff in drug treatment clinics in enhancing diagnosis and treatment of HCV-infected PWID. The cost-effectiveness of this intervention's implementation by avoiding the costly hospital setting was further demonstrated **[6].**

3. References to the research

Key papers (University of Nottingham UoA5 researchers, at the time of publication, are highlighted in bold)

1 **Irving WL**, Smith S, Cater R, Pugh S, Neal K, Coupland CAC, Ryder SD, **Thomson BJ**, Pringle M, Bicknell M, Hippisley-Cox J (2006). Clinical pathways for patients with newly diagnosed hepatitis C - what actually happens. *J of Viral Hepatitis 2006; 13: 264-271.* doi: 10.1111/j.1365-2893.2005.00698.x

2 McLauchlan J, Innes H, Dillon JF, Foster G, **Holtham E**, McDonald S, **Wilkes B**, Hutchinson SJ, **Irving WL** on behalf of the HCVRUK Steering Committee (2017). Cohort Profile: The Hepatitis C Virus (HCV) Research UK Clinical Database and Biobank. *International J of Epidemiology 2017; 46:1391-1391h*. doi:10.1093/ije/dyw362.

3 Foster GR, **Irving WL**, Cheung MCM, Walker AJ, Hudson BE, Verma S, McLauchlan J, Mutimer DJ, Brown A, Gelson WTH, MacDonald DC, Agarwal K on behalf of HCVRUK (2016). Impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. *J Hepatology 2016; 64(6): 1224-1231.* doi: 10.1016/j.jhep.2016.01.029

4 Wing PAC, Jones M, Cheung M, DaSilva S, Bamford C, Lee WJ, Aranday-Cortes E, Da Silva Filipe A, McLauchlan J, Smith D, **Irving WL**, Cunningham M, Ansari A, Barnes E, Foster GR (2019). Amino acid substitutions in genotype 3a Hepatitis C virus polymerase

protein affect responses to Sofosbuvir. *Gastroenterology 2019; 157(3):692-704.e9.* doi: 10.1053/j.gastro.2019.05.007

5 Lattimore S, **Irving WL**, Collins S, Penman C, Ramsay M (2014). Using surveillance data to determine treatment rates and outcomes for patients with chronic hepatitis C virus infection. *Hepatology 2014; 59: 1343-50.* doi: 10.1002/hep.26926

6 Ward Z, Reynolds R, Campbell L, Martin NK, **Harrison G**, **Irving WL**, Hickman M, Vickerman P (2020). Cost-effectiveness of the HepCATT intervention in specialist drug clinics to improve case-finding and engagement with HCV treatment with people who inject drugs in England. *Addiction 2020; 115(8):1509-21.* doi:10.1111/add. 14978

Grants:

7 2004-06, Department of Health, "Extension and consolidation of the Trent Cohort study of HCV patients", **Irving** PI, GBP120,377

8 2006, GlaxoSmithKline, "Trent Cohort study related to assessment of biomarker discovery", **Irving** PI, GBP120,000

9 2007, Pfizer Limited, "Trent Cohort Study related to assessment of liver biopsy fibrosis", **Irving** PI, GBP70,000

10 2011-15, Medical Research Foundation/Medical Research Council, "Establishment of a Resource for Long-Term Study of Hepatitis C Virus Infection in the UK – HCV Research UK", John MacLauchlan PI (University of Glasgow) and **Irving** Co-I, GBP1,608,704

11 2013-19, Medical Research Council, **"**Stratified Medicine to Optimise Treatment for Hepatitis C Virus Infection (STOP-HCV)", **Irving** Co-I, GBP4,168,144

12 2014-18, Department of Health Policy Research Programme, **"**Evaluation of interventions designed to increase diagnosis and treatment of patients with hepatitis C virus infection in primary care and drug treatment settings", GBP1,128,297, **Irving** PI

13 2015-17, Gilead Sciences Investigator Sponsored Research, "Real world outcomes of treatment of HCV-infected patients based on the use of Sofosbuvir", **Irving** PI, GBP116,650

14 2016-19, Gilead Sciences Investigator Sponsored Research, "Observational study of real world effectiveness of Sofosbuvir containing antiviral HCV regimens in cirrhotic patients infected with HCV in the UK national patient cohort HCV Research UK", **Irving** PI, GBP137,344

4. Details of the impact

Professor Irving's research has been instrumental in setting up the national infrastructure for the study and treatment of HCV in the UK. His studies provided evidence on epidemiology and disease progression as well as generating important findings to benchmark progress towards elimination of HCV by 2030, in accordance with WHO targets.

i HCVRUK **[2]** has enabled and improved the treatment of HCV patients, has informed national and international HCV patient treatment guidelines and has contributed to increased international uptake of DAAs:

i.i National and international patient benefit of DAAs with better treatment outcomes. In 2014, Professors Irving and McLauchlan successfully negotiated with the Department of Health the monitoring of the delivery, reimbursement and outcomes of the NHS EAP using HCVRUK. The co-chair of the Viral Hepatitis Advisory Group of NHS England at the time and national leader in HCV clinical management said *"…patients with such advanced liver disease were not able to wait for the formal licensing of the drugs…A key component of our argument for early access was the existence of the comprehensive monitoring system available through HCVRUK…Hence the existence of HCVRUK played a pivotal role in the EAP as a bridge between the NHS and the pharmaceutical companies, and ultimately had undoubted benefit to seriously ill patients."* **[S1].** Professor Irving and colleagues identified 806 patients with advanced liver disease as in most urgent need of the new DAAs, ahead of licensing. Of the 711 patients treated with known virological outcomes, 641 (90%) were successfully treated **[S2]**. Not only did the EAP describe and deliver the optimal care plan for very ill patients, but its clinical success was such that it led to the approval of DAAs and a rapid fall in HCV-associated mortality and liver transplantation in England. A 2019 PHE report states: *"Since the new DAA drugs have been available...a fall in the number of HCV-related liver transplants and deaths has been observed",* with a 38.9% decrease in transplants and 16.3% decrease in deaths from 2014 to 2017 **[S3]**.

DAAs used during the EAP were supplied by pharmaceutical companies Gilead Sciences Ltd, Bristol-Myers Squibb and Abbvie. Data collected by HCVRUK during the EAP demonstrated effectiveness and safety of the new DAAs **[3, S2]** and provided key epidemiology and patient information for NICE and NHS England to make decisions to treat certain patients with a combination of DAAs and other approved medicines. This data also encouraged clinicians across Europe and North America to treat HCV patients with these drugs, increasing international uptake of DAAs. Medical Director of Gilead stated: *"Without the HCVRUK database there would not only be a paucity of data on the seriousness of HCV infection in the UK but also a far smaller number of patients that had received treatment with the drugs that have been licensed in the past 5 years… the HCVRUK database played a valuable role in supporting our work to obtain NICE approval for the reimbursement of our new HCV medicines, and to provide evidence of the effectiveness of the medicines in clinical practice, thus supporting increased uptake… Following NICE approval … these data added to the body of evidence to give European clinicians confidence that the new medicines were effective in European patients"* **[S4].**

According to WHO, approximately 5,000,000 people globally had received DAA treatment for HCV by the end of 2017. WHO states that access to DAAs is revolutionising the prospect of ending HCV epidemics.

Additionally, HCVRUK and STOP-HCV provided a framework to deliver a phase 3 study of Sofosbuvir, a new candidate compound for the treatment of HCV by Gilead **[4]**. This study provided the evidence for a shorter treatment duration preferred by NHS England **[S4]**.

i.ii National and international guidelines for patient care were informed. The European Association for the Study of the Liver (EASL) guidelines cite the EAP and HCVRUK studies **[3** and others**]** to recommend the use of certain DAA combinations in patients since 2016 **[S5]**. The Asian Pacific Association for the Study of the Liver (APASL) cite the EAP in their recommendations **[S5]**. EASL and APASL guidelines inform the WHO on their recommendations for care and treatment of HCV patients. EASL guidelines inform NICE and Scottish Medicine Consortium (SMC) guidelines, which underpin the UK reimbursement strategy for diagnosis and treatment of HCV.

Evidence of the major nationwide collaboration achievement that HCVRUK represents is the recognition by the British Association for the Study of the Liver (BASL) with the 2019 Service Recognition Award to Professor Irving and his close collaborator Professor McLauchlan. The current chair of BASL said *"HCVRUK has been instrumental in understanding the epidemic of HCV infection and in helping in the efforts towards achieving HCV elimination… In addition to its direct impact on HCV, HCVRUK has had a lasting and much broader impact in establishing a model for collaborative working between scientists and clinicians from across the whole of the U.K."* **[S6].**

ii The study of the cascade of care improved HCV patient outcomes and informed guidelines for the treatment of HCV:

Professor Irving's study of the cascade of care in collaboration with PHE **[5]** was designed to better understand and improve engagement and retention in care of chronic HCV patients. The Head of Immunisation and Deputy Director of the National Infection Service at PHE said *"Professor Irving's cascade of care research has been a seminal piece of work which has been used to inform modelling estimates of prevalence of HCV in England, and the diagnosed and treated proportion since 2006 to date. The modelling estimates and estimating proportion treated are fundamental to monitoring progress towards elimination of HCV as a public health threat–a commitment to the WHO [HCV elimination] strategy that the UK government has made"* **[S7].**

An example of best practice that emerged from the cascade of care studies is 'reflex testing', which has now been implemented across England, with 65% of sentinel laboratories routinely undertaking this practice **[S8].** Reflex testing decreases patient drop-out and therefore improves patient outcomes and cost for the health provider.

"In recognition of his research credentials" **[S7]**, Professor Irving was invited to be independent chair for the National Strategic Group for Viral Hepatitis (May 2017 to present), the multiagency and multidisciplinary expert group that oversees the National Elimination Strategy (whose objective is the elimination of HCV infection in the UK by 2030). Irving's research data presented to the strategic group was essential to demonstrate that better

diagnosis and initiation of treatment of HCV patients by healthcare practitioners leads to improvement in outcomes for the HCV patients and is cost-effective for the healthcare commissioners. Professor Irving is also member of the PHE Hepatitis C Virus Resistance Group (2018-present) that published the *'Antiviral resistance testing in the management of hepatitis C virus infection'* guidance in November 2018. This document provides guidance to NHS clinicians for the stratification of HCV patients that present with infections resistant to DAAs **[S9]**.

iii The HepCATT study informed national and international guidelines and improved HCV patient outcomes:

According to PHE, injecting drug use is the most important risk factor for HCV infection in the UK, with one in every four people who inject drugs (PWID) infected with HCV in 2020. The number of PWID in England was last estimated in 2011 at over 100,000. Professor Irving specifically reviewed the care received by PWID who are also HCV-infected in the HepCATT study. HepCATT showed how the diagnosis, treatment pathways and cure of HCV positive PWID improves by investing in healthcare staff in the drug treatment clinics, without involving hospitals, an intervention that is also cost-effective **[6]**. *We Are With You* (formerly known as Addaction), a UK charity that works with drug, alcohol and prisons services and helped 130,000 people in 2019, collaborated with Professor Irving in the HepCATT study. As a result of this collaboration, they saw immediate benefits for the people involved in the study, with *"increased engagement of HCV-positive service users, reducing the gap between diagnosis and treatment…there was increased uptake of testing, referral to hepatology and initiation of treatment".* The charity also reports a longer-term benefit: *"the HepCATT study gave us a solid foundation… we were able to enhance the quality of HCV care across the continuum by improving service user outcomes, promoting safety, increasing user service satisfaction, and optimising combined resources"* **[S10]**.

Following Professor Irving's recommendations, PHE issued new policy and guidelines on World Hepatitis Day 2019 which highlight the HepCATT study and have led to the improvement of patient outcomes across the UK **[S11]**. The Head of Immunisation and Deputy Director of the National Infection Service at PHE said *'The HepCATT study is one of a few multicentre studies of complex interventions in drug service settings… Professor Irving's research is timely, relevant and patient and community focused… As more and more commissioners and providers adopt these pathways of care… we expect to see continued and increasing benefits from this research for patients in the UK and globally'* **[S7]**.

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) selected the HepCATT study to be included in a compilation of 11 examples of new models of care from 8 European countries for delivering testing and care to HCV positive PWID. This was also launched and showcased on World Hepatitis Day 2019 **[S12]**.

5. Sources to corroborate the impact (websites were last accessed on 18/01/2021)

S1 Corroborative statement: Clinical Lead of NHS England during the EAP.
S2 Presentation of the EAP results at the ECCIMD 2017 by Irving, ME0791 p43,44, web link
S3 PHE report: 'Hepatitis C in England 2019, working to eliminate Hepatitis C as a major public health threat'. P. 20, 21; Fig. 3 and 4, web link
S4 Corroborative statement: Medical Affairs Lead for Liver Diseases of Gilead Science Ltd.
S5 Combined 2018 EASL guidelines, page 27 ref 117, 118; 2016 APASL guidelines, ref 104
S6 Corroborative statement from president of BASL
S7 Corroborative statement: Head of Immunisation and Deputy Director of National Infection Service at PHE.
S8 Simmons, R, Ireland, G, Irving, W, et al. 'Establishing the cascade of care for hepatitis C in England—benchmarking to monitor impact of direct acting antivirals'. *J Viral Hepat*. 2018; 25: 482– 490. doi.org/10.1111/jvh.12844
S9 PHE guidance *'Antiviral resistance testing in the management of HCV infection',* web link
S10 Corroborative statement: Lead Clinical Nurse for Blood Borne Virus at *WeAreWithYou*.
S11 PHE evidence review: *'Hepatitis C: Interventions for patient case-finding and linkage to care'*. Seven of Irving's publications are referenced in p. 90, 91, 93, 95 and 96, web link
S12 EMCDDA report, Case Study 1, pages 13-19, web link