Institution: University of Glasgow (UofG)		
Unit of Assessment: UoA 1 (Clinical Medicine)		
Title of case study: Improving treatment and re-treatment outcomes in patients with chronic hepatitis C virus infection		
Period when the underpinning research was undertaken: 2012–2018		
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:**
(1) Prof. John McLauchlan (2) Prof. Emma Thomson (3) Dr Rob Gifford	(1) Professor (2) Clinical Senior Lecturer; Professor (3) Senior Research Fellow	(1) 2003–present (2) 2011–2018; 2019–present (3) 2013–present
Period when the claimed impact occurred: 2016–2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Patients with chronic hepatitis C virus (HCV) infection and advanced liver disease represent a severely ill sub-population of HCV patients. UofG was a founding partner of HCV Research UK (HCVRUK), a national clinical and scientific framework that enabled the NHS and pharmaceutical companies to deliver new life-altering direct-acting antiviral (DAA) drugs to this population, improving patient outcomes. HCVRUK findings now underpin international clinical guidelines on treatment options for this patient group. However, in 5% of all HCV patients receiving DAA drugs the treatment fails. UofG research delivered the operational workflow for a national HCV diagnostic service, which together with a UofG bioinformatic resource, ensures that patients receive a suitable alternative DAA.

2. Underpinning research

Establishing HCVRUK as the national infrastructure for HCV research

The MRC-UofG Centre for Virus Research has established an internationally recognised research profile for HCV. In 2007 **Prof. John McLauchlan** proposed establishing HCVRUK as a consortium of scientists and clinicians working to address key gaps in HCV research and disease management. HCVRUK was established in 2011 through an award of GBP1.92 million from the Medical Research Foundation to UofG [Grant A]. McLauchlan led HCVRUK, with the co-founding partner (Prof. Will Irving, University Nottingham) acting as the clinical sponsor. The grant involved over 30 co-applicants and connects major UK liver centres, universities, public health services and HCV charities involved in the management and support of HCV-infected patients. HCVRUK was subsequently extended to include 60 clinical sites through successful application for portfolio adoption by the NIHR Clinical Research Network.

Since March 2012, HCVRUK has integrated a biobank (hosted at UofG) with a bespoke clinical research database (hosted at University of Nottingham) to collate samples and clinical information from approximately 12,000 patients recruited from across the UK. With over 150,000 samples, the biobank is one of the largest HCV resources worldwide and supports clinical and basic research [3.1]. Between 2012–2019, HCVRUK has provided the clinical framework for the major objectives of STOP-HCV, a GBP5.2M MRC-funded, multicentre programme hosted at the University of Oxford [Grant B]. The contribution of HCVRUK to STOP-HCV includes providing clinical data and samples, and ethical support to recruit a bespoke cohort. **Prof. McLauchlan** co-led work strand 1 of STOP-HCV — provision of well-characterised patient samples and metadata from HCVRUK. **Prof. Emma Thomson** led on the development of HCV whole-genome sequencing methods.

Understanding treatment responses to HCV antiviral drugs

HCVRUK and UofG research has occurred against the backdrop of the transformative introduction and increased use of DAA drugs to treat HCV; as such it has been well-placed to undertake 'real world' studies to monitor responses to these drugs. In particular this included patients with advanced decompensated liver disease—where the liver has limited capacity to function—who were at significant risk of death or irreversible damage within 1 year, but in whom the benefits of DAA treatment was unknown. In 2014, the NHS England announced an Expanded Access Programme (EAP) to enable patients with advanced decompensated liver disease, or who were interferon-intolerant (the standard treatment for HCV prior to DAA drugs),

to receive DAA drugs before their formal approval by the National Institute for Health and Care Excellence (NICE). Around 800 patients (>90% of whom were recruited into HCVRUK) received treatment with DAA drugs across approximately 30 clinical sites in England—one of the largest cohorts of HCV-infected patients with advanced liver disease worldwide. HCVRUK provided a national framework that enabled patient recruitment to occur at all sites involved in the EAP, as well as the collection and release of clinical data and samples to monitor treatment outcomes. The HCVRUK framework also led to two high-profile papers co-authored by **McLauchlan** [3.2, 3.3], which addressed the effectiveness of DAA drugs in advanced liver disease and reported the first real-world evidence that the drugs were well tolerated and achieved high cure rates among patients with decompensated liver disease. A further study from the EAP, led by **McLauchlan** and **Thomson**, highlighted the difficulties in achieving successful therapeutic outcomes for DAA-based therapy for patients infected with rare HCV subtypes common in Africa and among migrant populations [3.4]. UofG developed and deployed a pipeline and workflow for next-generation sequencing to support these studies (outlined below).

A new diagnostic approach to identifying HCV genotype and resistance

Despite the success of DAA drugs, their use can be limited by mutations to viral RNA that confer resistance. In 2016, **Thomson** led a study that developed a target-enrichment approach to detecting low-level, resistance-associated substitutions (RAS) among patients with HCV infection not successfully cured by DAA drugs. Conducted in collaboration with STOP-HCV, this study produced a custom-designed probe set for target enrichment that enables rare HCV strains and subtypes to be sequenced and also validated the probe set and their use [3.5]. UofG researchers (**Dr Rob Gifford**, **Thomson**, **McLauchlan**) also designed and implemented a bioinformatic platform for HCV sequence data (HCV-GLUE). Constructed to systematically download and store all publicly available HCV sequences (>500 base pairs in length), this platform holds over 80,000 sequences (90% of those currently available). HCV-GLUE has enabled any RAS to be identified in uploaded HCV sequence data for all genotypes (n=8) and subtypes (n=84) [3.6].

3. References to the research

1. **McLauchlan, J.** *et al*. (2017). Cohort profile: The Hepatitis C Virus (HCV) Research UK clinical database and biobank. *Int J Epidemiol*., 46(5):1391-1391h (doi: 10.1093/ije/dyw362).
2. Foster GR, Irving WL, Cheung MC, Walker AJ, Hudson BE, Verma S, **McLauchlan J.** *et al*. (2016). Cohort study of the impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. *J Hepatol*., 64: 1224-1231. (doi: 10.1016/j.jhep.2016.01.029).
3. Cheung MCM, Walker AJ, Hudson BE, Verma S, **McLauchlan J**. *et al*. (2016). Outcomes after successful direct-acting antiviral therapy for patients with chronic hepatitis C and decompensated cirrhosis. *J Hepatol*., 65: 741-747. (doi: 10.1016/j.jhep.2016.06.019).
4. Da Silva Filipe, A, […] **McLauchlan J**, **Thomson EC**. (2017). Response to DAA therapy in the NHS England Early Access Programme for rare HCV subtypes from low and middle income countries. *J Hepatol*., 67: 1348-1350. (doi.org/10.1016/j.jhep.2017.06.035)
5. **Thomson, E**, […], **McLauchlan J**, *et al*. (2016) Comparison of next generation sequencing technologies for the comprehensive assessment of full-length hepatitis C viral genomes. *J Clin Microbiol*., 54: 2470-84. (doi: 10.1128/JCM.00330-16).
6. Singer, J.B., **Thomson E.C.**, **McLauchlan, J**., Hughes, J., **Gifford, R.J.** (2018) GLUE: A flexible software system for virus sequence data. *BMC Bioinform*., 19: 532. (doi: 10.1186/s12859-018-2459-9)

Grants:

A. HCV Research UK: Establishment of a Resource for Long-Term Study of Hepatitis C Virus Infection in the UK, Medical Research Foundation, GBP1.92million (2013–2015) PI: **J McLauchlan** (Grant # C0365)
B. STOP-HCV: Stratified Medicine to Optimise Treatment for Hepatitis C Virus Infection, Medical Research Council, GBP381,000 to UofG (2013-2018) PI: E Barnes (University of Oxford); Co-PIs **J McLauchlan** and **E Thomson**
C. Additional Support for HCV Research UK, Pharmaceutical Industry (various), GBP800,000 (2013-2019). PI: **J McLauchlan**.

4. Details of the impact

HCV infection is a leading cause of chronic liver disease, decompensated cirrhosis and liver cancer in the UK. As co-founder of HCVRUK, the UofG has played a pivotal role in targeting new DAA drugs to HCV patients, particularly those with advanced decompensated liver disease (**impact 1**); and has changed international clinical guidelines to recommend such treatment (**impact 2**). However, not all DAA treatment is successful. By developing new clinical methodologies and patient-stratification tools, UofG has also helped to operationalise national re-treatment pathways to address treatment failure caused by rare HCV subtypes or drug-resistant variants (**impact 3**). The HCVRUK biobank has also provided a resource to industry (**impact 4**).

Impact 1: HCVRUK enabled treatment and improved outcomes of HCV patients

The EAP supplied life altering DAA drugs to 800 patients with advanced decompensated liver disease, including drugs awaiting formal NICE approval. During 2014–2016, the HCVRUK framework provided the mechanism by which NHS England was able to evaluate the delivery and outcomes of the EAP, and reimburse clinical sites tasked with delivering this programme [3.1].

The co-chair of the Viral Hepatitis Advisory Group of NHS England at the time (and current National Clinical Chair for the Hepatitis C) said, "*A central concern within the NHS was how this unlicensed use of drugs in profoundly ill patients could be monitored and the pharmaceutical drug manufacturers expressed concern about unregulated use … **a key component of our argument for early access was the existence of the comprehensive monitoring system available through HCVRUK**. … [which] **played a pivotal role in the Early Access Programme as a bridge between the NHS and the pharmaceutical companies, and ultimately had undoubted benefit to seriously ill patients**"* [A].

The EAP was an acknowledged clinical success, despite the seriousness of disease in these individuals. **Of the 711 patients with known outcomes, 90% were successfully treated: 82% (n=583) achieved a sustained response and 8% (n=58) were successfully re-treated following treatment failure** [B]. Follow-up data from 602 patients treated in the EAP cohort also revealed the benefit of DAA treatment success versus treatment failure in terms of mortality—92.7% versus 63% survival, respectively. Treatment improved liver function especially in those with decompensated disease and halved the rate of significant deterioration [C]. Major pharmaceutical companies (Gilead, Bristol-Myers Squibb and AbbVie) provided GBP17 million of DAA drugs to the EAP and received summary data that allowed them to evaluate real-world effectiveness for the most in-need patients—a population for whom very little clinical trial data was available at the time. The Medical Director of Gilead said, "***This data was hugely influential in encouraging clinicians across Europe and North America to consider treating such patients for their HCV as opposed to just managing their symptoms***" [D]. The President of the British Association for the Study of the Liver, said, "*At the beginning of this new era of treatment, HCV Research UK played a pivotal role in assessing the effectiveness of the drugs in UK patients with serious liver disease. This starting point was the basis for current efforts aimed at achieving HCV eradication in the UK*" [E].

Impact 2: Changing international treatment guidelines

The findings of HCVRUK research now support treatment recommendations for the use of DAA drugs to treat patients with advanced decompensated liver disease:

- Since 2016, the European Association for the Study of the Liver (EASL) guidelines cite HCVRUK/UofG research [3.2, 3.3] to support the use of sofosbuvir/ledipasvir/ribavirin combination therapies in groups with decompensated liver disease. The 2016 Asia-Pacific Association for the study of the liver (APASL) likewise cite EAP data [3.2] to support use of these drugs in this patient group [F].
- Thomson represented the European region on the World Health Organization committee that in 2018 produced the HCV treatment guidelines. These guidelines cite UofG work on rare viral subtypes [3.4] as background, highlighting the lack of understanding of HCV genotype distribution in many parts of the world [G].

EASL guidelines set the tone for national guidelines, such as NICE and the Scottish Medicines Consortium, which underpin the UK reimbursement strategy for HCV testing, diagnosis and treatment. England was one of the first countries worldwide to introduce treatment for patients with advanced liver disease. A Public Health England (PHE) report 'Hepatitis C in England 2020' states that during 2015–2019, 38,784 individuals initiated treatment as part of the UK's national DAA treatment programmes. Of these, 26% (12,646) had advanced liver disease (cirrhosis), including 1,226 patients with decompensated liver disease who may not have been prioritised for treatment without the work of the EAP and HCVRUK.

Impact 3: Providing a pathway to HCV re-treatment with DAAs

Despite the effectiveness of new DAA drugs, NHS National HCV Registry data from 2018 show that 4.8% of these treatments fail, rising to 11% among patients with decompensated liver disease. Treatment failure prolongs the malignant pathology of HCV disease (which progresses to liver failure in 6.5% patients each year) and substantially reduces patients' quality of life. It also perpetuates the costs to the NHS of managing chronic HCV disease, and increases the risk of onward spread of infection between people.

Treatment failure is partly due to DAA resistant HCV variants that emerge during treatment, but also due to naturally occurring rare HCV subtypes (gt1l and gt4r) that do not respond optimally to particular DAA combinations. These subtypes are most common among UK residents from Black/African/Caribbean/Black British ethnic groups who may have contracted HCV prior to arrival in the UK [3.4] and account for 20% of patients not responding to DAAs. Retreatment is possible with an alternative DAA combination but should be informed from knowledge of the previously prescribed treatment.

International guidelines offer no consensus on HCV resistance testing; nonetheless, UofG researchers have continued to help develop guidelines and workflows to support this issue in a UK context. In 2018, McLauchlan and Thomson were part of the PHE HCV resistance committee that contributed data on the molecular characteristics and analysis of DAA resistant variants and treatment outcomes of rare subtypes. This committee developed new PHE guidance (2019) for clinicians setting out requirements for DAA resistance testing in HCV management pathways, especially for patients undergoing re-treatment [H]. The implementation of resistance testing in PHE is being facilitated by a workflow built on UofG research (outlined below).

Delivery of a new HCV diagnostic platform

Successful treatment of DAA-resistant HCV requires additional information on the specific HCV subtypes and resistance variants present among affected patients. UofG research has provided an operationalizable HCV diagnostic workflow for detecting rare HCV subtypes [3.5]. The findings enabled PHE to implement a new national HCV whole-genome sequencing (WGS) service, which has received ~GBP250,000 in funding towards additional infrastructure and staff costs [I]. The WGS service implements the UofG workflow and the probe-sets that were validated using samples from the HCVRUK biobank at UofG, including African rare subtypes, enabling confidence in the platform. Launched in July 2019, the WGS service is supporting the rollout of DAA treatment by NHS England through designated Operational Delivery Networks, processing an average of 40 patient samples per week, directing treatment and re-retreatment pathways for patients infected with DAA-resistant HCV [I].

Complementing the WGS service is the adoption of HCV-GLUE (http://hcv-glue.cvr.gla.ac.uk/, see section 2) by PHE and NHS Greater Glasgow & Clyde health board to identify HCV subtypes and resistant variants. HCV-GLUE is the first HCV sequence analysis resource based on EASL guidelines. It provides a unique, publicly available online resource, which draws on known resistance variants identified in clinical trials. As such, HCV-GLUE helps to translate diagnostic screening into clinical practice by linking to defined treatment guidance for any specific resistance variant. To facilitate this linking, Prof. Thomson worked with PHE in 2017 to establish the PHE HCV Resistance Group, a clinical committee of 15 UK clinicians and clinical virologists, to assess the treatment options for a range of resistant HCV variants that HCV-GLUE

can identify, and to offer guidance on data interpretation for clinicians treating HCV-infected patients. The HCV-GLUE software is also integrated into the operational workflow of the PHE WGS service: "*This has resulted in a clinical standard, robust and up to date genotypic interpretation tool, which is superior to existing publicly available options"* – Head, Antiviral Unit, PHE [I]. Between 1st November 2018–31stJuly 2020 the tool has been run 2,612 times by users in 22 countries to support genotyping and drug resistance analysis [J]. Offline installations of HCV-GLUE are also used to support clinical decision making by the Norwegian Institute of Public Health and Copenhagen University Hospital, Denmark [K].

Impact 4: Access to the HCVRUK biobank benefits industry

The Medical Director at Gilead Sciences Inc. said, "*The HCV Research UK database played a valuable role in supporting our work to obtain National Institute for Health and Care Excellence (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*". Furthermore, the biobank stored approximately 42,000 samples from the phase 3 BOSON trial, conducted by Gilead, for use by STOP-HCV: "*HCVRUK in collaboration with the STOP-HCV consortium were able to provide the framework that enabled the rapid delivery of a phase 3 study (BOSON) of one of our new medicines (sofosbuvir). This provided the evidence supporting a shorter treatment duration, preferred by NHS England and UK clinicians, but for which very little data was available at the time of the launch of the medicine"* [D, L].

Helena Biosciences used HCVRUK biobank samples to validate their Glyco Liver Profile assay—a non-invasive test to detect and stage liver fibrosis and cirrhosis. The Clinical Applications Specialist at Helena said, "*The University of Glasgow and HCV Research UK were instrumental in acquiring a large volume of HCV samples to adequately represent this* [chronic liver disease] *population. Expert clinical analysis of the biopsy data provided alongside venous blood samples were an essential part of completing the validation of the original method."* The samples enabled Helena Biosciences to define the cut-off values that correlate with liver disease stages—to differentiate compensated and decompensated cirrhosis and to identify patients at risk of hepatocellular carcinoma. Launched in December 2019, the Glyco Liver Profile assay is expected to help reduce the number of biopsies required, and the risks associated with this procedure, and to enable increased monitoring of existing patients [M].

5. Sources to corroborate the impact [PDFs provided unless otherwise indicated]

A. Testimony: NHS England, National Clinical Lead for HCV
B. Data from ESCMID presentation (Arends & Irving, April 2017, see slide 43/44)
C. Johnson *et al*. (2020) Impact of direct acting antiviral agents on liver function in patients with chronic hepatitis C virus infection. *J Viral Hepat*. 28:168–176 (doi: 10.1111/jvh.13408)
D. Testimony: Gilead Sciences, Medical Director
E. Testimony: British Association for the Study of the Liver, President
F. International guidelines: (1) EASL guidelines on hepatitis C 2016, 2017, 2018 (2018 guideline: citing [3.2] as ref.117, p.27; and [3.3] as ref.118, p.27); (2) APASL guidelines for hepatitis C 2016: citing [3.2] as ref.104, p.716/717 (recommendation #8).
G. World Health Organization (2018) Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection
H. (1) PHE: Antiviral resistance testing in the management of hepatitis C (Dec 2018); also available as (2): Bradshaw *et al*. (2019) Consensus recommendations for resistance testing in the management of chronic hepatitis C virus infection: Public Health England HCV Resistance Group. *J Infect*. 79(6):503-512. (doi: 10.1016/j.jinf.2019.10.007)—cites UofG papers: [3.5] and [3.6] to support analysis approach recommendations.
I. Testimony: Public Health England, Head of Antiviral Unit
J. HCV-GLUE statistics provided by UofG-MRC CVR Bioinformatics team
K. International GLUE-HCV use: (1) Copenhagen University Hospital; and (2) Norwegian Institute of Public Health
L. UofG/HCVRUK material transfer agreement to provide clinical samples to STOP-HCV and Gilead Sciences Inc. as part of BOSON trial (20th November 2013)
M. Testimony: Helena Biosciences Europe: Clinical Applications Specialist