Institution: University of Plymouth

Unit of Assessment: UoA1

Title of case study: Reducing mortality from Hepatitis C virus

Period when the underpinning research was undertaken: 2013 – 31.07.20

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:
Professor Matthew Cramp	Professor of Hepatology	2013-present

Period when the claimed impact occurred: 01.08.2013 – 02.11.20

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

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

Hepatitis C virus (HCV) infection is a major cause of advanced liver disease, cirrhosis, liver cancer and death. Before 2015, treatment was complex, poorly tolerated and frequently ineffective. Professor Cramp has been a leader in the field of clinical trials of new HCV-specific anti-virals (proving they cure HCV infection in over 95% of cases) and in shaping national and regional policy to design and deliver the clinical services needed for widespread adoption of new treatments. These developments have been so successful that the number of UK cases initiating treatment leapt from 6400 in 2013/14 to 15,200 in 2018/19, mortality has fallen sharply (down by 18.8% from 468 in 2015 to 380 deaths in 2018), and elimination of HCV as a public health problem in the UK by 2025 is achievable.

2. Underpinning research (indicative maximum 500 words)

HCV is a major cause of liver-related mortality in the UK and globally affecting 2% of the worldwide population. Death from advanced liver disease and liver cancer typically occurs after several decades of infection with HCV, and mortality from HCV related liver disease had been rising sharply over the last two decades. Treatments previously relied on interferon and ribavirin which were unpleasant, poorly tolerated and ineffective, especially in those with more advanced liver disease.

Professor Cramp is a clinical academic hepatologist actively researching HCV treatments and strategies for HCV prevention and protection for 25 years. Professor Cramp contributed to multiple clinical studies, being involved in study design through to study delivery, and in ensuring the pipeline of new treatments progressed rapidly from discovery into clinical trials and clinical practice. The clinical trials swiftly established which of these drugs and drug combinations were the most potent and the best tolerated. The next step was to look at how to most effectively use these drugs to reduce mortality and deal with the epidemic of liver disease, especially as they were initially very expensive. Through a combination of mathematical modelling to describe the huge beneficial impact of widely available treatment, lobbying and petitioning for funding, and developing services capable of successfully treating large numbers of patients, the HCV

epidemic in the UK has been significantly altered with sharp falls in mortality, a rapid rise in treatment numbers and a huge leap in the number of people cured of their infection.

Professor Cramp's research in the field of HCV spans (a) investigation of new improved treatments, (b) defining and modelling HCV disease progression and the impact of treatment, (c) a laboratory based program of work looking at individuals with natural resistance to HCV.

(a) Investigation of new improved treatments [3.1 & 3.2]

- Professor Cramp was involved in over 20 clinical trials of new drugs in the HCV drug development pipeline, including all the major phase III registration studies for the drugs now in global use. As Principal Investigator he led the recruitment of a large number of patients from across the SW Peninsula and oversaw study delivery with a team of research nurses and clinical fellows delivering studies to time and recruitment target.
- Professor Cramp contributed to study design working as an expert advisor on national and international advisory boards to key pharmaceutical companies involved in drug development (including Gilead, Merck, AbbVie, Boehringer Ingelheim, Janssen)

(b) Defining and modelling HCV disease progression [3.3 -3.5]

- Professor Cramp was lead author on one of the early works predicting (accurately) the rapid fall in mortality from hepatocellular carcinoma and end stage liver disease achievable in the UK with the early and widespread introduction of new treatments, but noting that achieving this reduction required both increased case detection and treatment numbers.
- Professor Cramp has been on the steering committee for HCV Research UK since its inception – an MRC-funded large national HCV registry – that has helped define natural history
- Professor Cramp has worked with the Centre for Disease Analysis and the Polaris Observatory assessing the current and future disease burden from viral hepatitis globally and contributed to papers modelling economic impact and the impact of strategies aiming for elimination.

(c) A laboratory based program of work looking at individuals with natural resistance to HCV [6]

- Some injection drug users do not become HCV infected despite repeated exposure through drug use, demonstrating natural resistance to HCV infection. Professor Cramp has led a program of study identifying a number of immunological, genetic and metabolic factors that can protect from HCV infection.

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

The following references are a representative selection illustrating the comprehensive body of work described above.

(a) Investigation of new improved treatments:

3.1 Elbasvir/grazoprevir and sofosbuvir for hepatitis C virus genotype 3 infection with compensated cirrhosis: A randomized trial. Foster GR, Agarwal K, Cramp ME, Moreea S, Barclay S, Collier J, Brown AS, Ryder SD, Ustianowski A, Forton DM, Fox R, Gordon F, Rosenberg WM, Mutimer DJ, Du J, Gilbert CL, Asante-Appiah E, Wahl J, Robertson MN, Barr E, Haber B. Hepatology. 2018 Jun;67(6):2113-2126

3.2 Sofosbuvir/velpatasvir for 12 weeks in hepatitis C virus-infected patients with end-stage renal disease undergoing dialysis. Borgia SM, Dearden J, Yoshida EM, Shafran SD, Brown A, Ben-Ari Z, **Cramp ME,** Cooper C, Foxton M, Rodriguez CF, Esteban R, Hyland R, Lu S, Kirby BJ, Meng A, Markova S, Dvory-Sobol H, Osinusi AO, Bruck R, Ampuero J, Ryder SD, Agarwal K, Fox R, Shaw D, Haider S, Willems B, Lurie Y, Calleja JL, Gane EJ. *J Hepatol. 2019 Oct;71(4):660-665*

(**b) Defining and modelling HCV disease progression:**

3.3 Modelling the impact of improving screening and treatment of chronic hepatitis C virus infection on future hepatocellular carcinoma rates and liver-related mortality. **Cramp ME**, Rosenberg WM, Ryder SD, Blach S, Parkes J. BMC Gastroenterol. 2014;14:137

3.4 HCV treatment rates and sustained viral response among people who inject drugs in seven UK sites: real world results and modelling of treatment impact. Martin NK, Foster GR, Vilar J, Ryder S, **Cramp ME,** Gordon F, Dillon JF, Craine N, Busse H, Clements A, Hutchinson SJ, Ustianowski A, Ramsay M, Goldberg DJ, Irving W, Hope V, De Angelis D, Lyons M, Vickerman P, Hickman M. *J Viral Hepat. 2015 Apr;22(4):399-408*

3.5 Global Prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Polaris Observatory HCV Collaborators. *Lancet Gastroenterol Hepatol. 2017 Mar;2(3): 161-176*

(c) A laboratory based program of work looking at individuals with natural resistance to HCV

3.6 Exploration of potential mechanisms of hepatitis C virus resistance in exposed uninfected intravenous drug users. Shawa IT, Felmlee DJ, Hegazy D, Sheridan DA, **Cramp ME**. J Viral Hepat. 2017 Dec;24(12):1082-1088

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

Elimination of viral hepatitis by 2030 is one of the UN Sustainable Development Goals (target 3.3). Through the comprehensive body of research over two decades, Professor Cramp has enabled the widespread availability of treatments to HCV patients in the UK, which has been called “one of the outstanding NHS success stories of the last decade” [5.7], and the country is acknowledged to be ‘on target’ for the WHO-goal of elimination by 2030. More widely, many of the countries that have implemented programmes have been encouraged by the work and organisation of the UK scheme.[5.8]

New Treatments for HCV rapidly assessed

By contributing to good study design, rapid recruitment to clinical trials and the adoption of 12 week post treatment viral clearance as a key study endpoint predicting sustained viral response, Professor Cramp helped to ensure that new treatments could be accurately and reliably assessed for efficacy much faster than before. This was crucial with a large drug pipeline and ensured that the most effective drugs were granted regulatory approval rapidly to facilitate earlier treatment for all those infected. Once licensed, the pressing clinical need and large market for highly effective HCV drugs led to the three most commercially successful new drug launches in history with combined US sales of over $22 billion in their first 12 months from launch [5.1].

New Models of HCV treatment confirm their potential impact on global prevalence

The data obtained from clinical trials provided a strong evidence base for new treatments, and by contributing to the mathematical modelling of who to treat, when to treat and how many to

treat, Professor Cramp was able to help confirm that highly effective therapy could make a major impact on the whole HCV pandemic**.** It now required political and professional effort to obtain the funding and design the services needed to scale up treatment.

Changes to Policy & Medical Guidelines ensure this impact is delivered

Professor Cramp has sat on the Lancet Commission for Liver Disease since its inception and has led the viral hepatitis recommendations in each of the Lancet Commission papers. The first Lancet report in 2014 [5.2] made a recommendation for the widespread use of the new HCV treatments to achieve elimination of HCV in the UK by 2030, pre-dating the 2016 WHO report "Global Health Sector Strategy on viral hepatitis, 2016-2021 - Towards Ending Viral hepatitis" which made this a global goal. As an expert advisor to NICE, Professor Cramp enabled the transformation of national policy with NICE approval for the first wave of fixed dose combination HCV drugs granted in November 2015 [5.3]. Professor Cramp contributed to national policy and service design as Treasurer (2012-2016) then President (2017-2019) of the British Association for the Study of the Liver (BASL) and as a clinical expert representative on the Hepatobiliary and Pancreatic Clinical Reference Group (HPB CRG – advisory body to NHS England specialised commissioning, 2013-date). Through specialised commissioning and advised by the HPB-CRG, NHS England agreed to fund the use of new HCV drugs in 2015, initially for very advanced disease only and then, following NICE approval, for general use, and established 22 operational delivery networks (ODNs) to facilitate treatment upscaling. The ODNs were modelled on the managed clinical network that Professor Cramp established for the SW Peninsula as early as 2004. Professor Cramp led the successful 2016 submission to establish and lead the Peninsula HCV ODN and has led it since inception.

Reduced HCV mortality

The policy of treating the most advanced disease patient first has delivered a rapid fall in mortality from end stage liver disease from HCV and a rapid fall in the number of patients requiring liver transplantation for HCV related liver disease. Deaths had been steadily rising until 2015 when 468 people died but have since fallen by 18.8% with 380 deaths reported in 2018 [5.4]. The number of individuals being listed for liver transplant for HCV fell from an average of 135 / year in the years 2009-2014 to just 63 in 2017 and 75 in 2018 [5.5]. The fall in deaths matches closely that predicted by the mathematical models that helped shape policy (3.3, 3.4, 3.5) [5.6]. The HCV treatment services and the clinical network model adopted has been very successful at scaling up treatment numbers to enable NHS England to target elimination of HCV by as early as 2025.

Reduced HCV prevalence and elimination of HCV by 2025

Public Health England estimates suggest that with the advent of new treatments, the prevalence of chronic HCV had fallen from around 143,000 people (95% credible interval 123,000-161,000) in 2015 to around 113,000 (95% credible interval: 95,000, 132,000) in 2018 [5.3].

Increased treatment numbers

Across the UK treatment initiations from 2009 -14 remained relatively stable at around 6,400 initiations per year (6,390; Range: 6,130, 6,808) rising dramatically to 15,200 in 2018/19 [5.4] Between 2015 and 2020 the Peninsula HCV ODN led by Professor Cramp has treated over 1500 people with HCV infection, almost tripling annual treatment numbers from 150 to over 400 and has delivered cure rates of well over 90%. This increase in treatment numbers and cure

rates has been achieved even in the most socially disadvantaged groups (homeless, drug users, migrant populations and prisoners).

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

5.1 The industry's biggest drug launches. Urquhart, L. *Nat Rev Drug Discov* ***17,*** *855 (2018). https://doi.org/10.1038/nrd.2018.209*

5.2 Addressing liver disease in the UK: a blueprint for attaining excellence in health care and reducing premature mortality from lifestyle issues of excess consumption of alcohol, obesity, and viral hepatitis. Williams et al. *Lancet. 2014 Nov 29;384(9958):1953-97*

5.3 Ledipasvir–sofosbuvir for treating chronic hepatitis C. Technology appraisal guidance Published: 25 November 2015 nice.org.uk/guidance/ta363 *– see page 82*

5.4 Hepatitis C in the UK 2019 – Public Health England (see: Hepatitis_C_in_the_UK_2019_report.pdf , pages and 21-22 and 23-26)

5.5 Hepatitis C in England 2020 – Public Health England - (see: Hepatitis C in England 2020 report, *pages 32-33)*

5.6 Strategies to manage hepatitis C virus (HCV) disease burden. Wedemeyer et al. *J Viral Hepat. 2014 May;21 Suppl 1:60-89. doi: 10.1111/jvh.12249.*

5.7 Testimonial from Professor Graham Foster National Clinical Lead for HCV at NHS England and Chair of the HPB CRG

5.8 Testimonial from Professor Roger Williams as Chair of the Lancet Commission on Liver Disease