Institution: King's College London		
Unit of Assessment: 4		
Title of case study: Preventing deaths from heroin and other opioid overdose with Take Home Naloxone		
Period when the underpinning research was undertaken: 2001-2020		
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 Sir John Strang	Professor of Addictions	01/01/1993- present
Dr Rebecca McDonald	Post-Doctoral Researcher (previously PhD student)	27/03/2019- present
Professor Joanne Neale	Professor of Addictions Qualitative Research	17/06/2013- present
Period when the claimed impact occurred: 2014-2020		
Is this case study continued from a case study submitted in 2014? Y		

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

Naloxone saves lives by reversing the effects of opioid overdose. King's researchers recognised that overdoses of heroin/opioids are most life-threatening in community settings where medical staff are absent, and pioneered the concept of pre-providing naloxone to laypeople, known as Take-Home Naloxone (THN). Our research led to the development of a medically approved naloxone nasal spray as a safer, easier mode of administration than injection. This created a step-change in the wider provision of naloxone. King's evidence supported the United Nations (UN) and World Health Organisation (WHO) endorsements of THN and recommendations calling for its wider provision globally, and our research underpins training on how to administer THN. Over 23 countries have now implemented THN programmes, with the US alone having committed an extra $180 million funding. King's research has led to increased distribution of this intervention across the world so that opioid users, carers and families have it ready for when they need it, to save lives.

2. Underpinning research

Currently 58 million people use opioids annually (United Nations Office of Drugs and Crime (UNODC)), and each year approximately 120,000 people die around the world from an opioid overdose (WHO), with deaths up 71 per cent over the last decade (UNODC). Naloxone is a well-established emergency medicine which blocks opioid receptors in the brain, rapidly reversing heroin/opioid overdose. It saves lives by preventing respiratory failure, the leading cause of death from opioid overdose, most of which typically occur in the community, where there is no medical naloxone and emergency medical care may arrive too late. Robust evidence has been vital to overcome complex and value-laden barriers to using naloxone. King's research underpinned the ground-breaking concept of THN. This provides naloxone to laypeople including people who use opioids (PWUO), carers and families, for use whenever and wherever overdose occurs. This case study is a continuation of a 2014 case study featuring King's work establishing the effectiveness of injectable THN. Since then, our research has focussed on increasing the availability of THN though the development of a nasal spray, and on how training improves the implementation of the THN approach.

King's research showed that provision of THN prevents opioid overdose deaths.

Having been the first to demonstrate the feasibility and effectiveness of THN with PWUOs (2001), King's 2016 systematic review and analysis of 22 eligible further THN studies established that THN is an effective intervention to reduce deaths from opioid overdoses **(1)**.

King's highlighted the benefits of training potential users of Take-Home Naloxone. KCL research established that training PWUOs in overdose management and naloxone administration improved knowledge and confidence to administer naloxone **(2).** In a subsequent randomised trial on training family members to administer THN, King's researchers found that those who had received the training and witnessed an overdose, were able to mobilise skills, knowledge and competency to administer naloxone **(3).** King's researchers also led on a qualitative study embedded in a randomised THN intervention trial conducted in New York which identified high levels of post-training competence among PWUO, effective actions and successful reversals at overdose emergencies **(4).**

King's identified the need for non-injectable Naloxone as safer and more acceptable than injectable forms of delivery. Traditionally, injectable THN kits contain pre-filled syringes with a dilute concentration of naloxone. King's researchers found dilute naloxone was being diverted for use with an improvised nasal spray adapter in community and in medical settings. They demonstrated this practice risked administering a sub-therapeutic naloxone dose potentially insufficient to reverse the effects of an overdose **(5)**. King's also showed that those receiving injectable naloxone often experience acute withdrawal symptoms after administration, leading to reluctance to use THN **(6)**. Together these findings made a strong case for rigorous testing of new, safer and more acceptable delivery paradigms, such as nasal spray designed for purpose.

King's researchers led the field in the development and testing of a safe and efficacious nasal naloxone spray. King's collaborated with the international company Mundipharma to develop a purpose-manufactured, concentrated nasal naloxone spray suitable for layperson use. This involved proof-of-concept followed by testing the pharmacokinetics of three formulations of nasal spray doses to find the most effective dose for maintained reversal of opioid overdose **(7)**.

3. References to the research

1. **McDonald, R.,** & **Strang, J**. (2016). Are take-home naloxone programmes effective? Systematic review utilizing application of the Bradford Hill criteria. *Addiction*, *111*(7), 1177-1187. doi: 10.1111/add.13326
2. **Strang, J**., **Manning, V**., **Mayet S, Best D, Titherington E, Santana L, Offor E,** & **Semmler, C**. (2008) Overdose training and take-home naloxone for opiate users: prospective cohort study on knowledge and attitudes and subsequent management of overdoses. *Addiction*, 103, 1648-1657. doi: 10.1111/j.1360-0443.2008.02314.x
3. **Williams, A. V**., **Marsden, J**. and **Strang, J**. (2014), Training family members to manage heroin overdose and administer naloxone: randomized trial of effects on knowledge and attitudes, *Addiction* 109, 250–259. DOI: 10.1111/add.14510
4. **Neale, J**, Brown C, Campbell ANC, Jones JD, Metz VE, **Strang J**. & Comer SD (2019) How competent are people who use opioids at responding to overdose? Qualitative analyses of actions and decisions taken by lay first-responders during overdose emergencies. *Addiction* 114(4), 108-118. doi: 10.1111/add.14510
5. **Strang, J**., **McDonald, R**., **Tas, B**., & **Day, E**. (2016). Clinical provision of improvised nasal naloxone without experimental testing and without regulatory approval: imaginative shortcut or dangerous bypass of essential safety procedures? *Addiction*, 111, 574-582 doi: 10.1111/add.13209
6. **Neale, J**, & **Strang, J**. (2015) Naloxone—does over-antagonism matter? Evidence of iatrogenic harm after emergency treatment of heroin/opioid overdose. *Addiction*, 110, 1644-1652 DOI: 10.1111/add.13027
7. **McDonald, R**., Lorch, U., Woodward, J., Bosse, B., Dooner, H., Mundin, G., ... & **Strang, J**. (2017). Pharmacokinetics of concentrated naloxone nasal spray for opioid overdose reversal: Phase I healthy volunteer study. *Addiction*, 113, 484-493. doi: 10.1111/add.14033

4. Details of the impact

Against a backdrop of escalating opioid use and overdose deaths, King's research has built on our 2014 case study to improve THN implementation and availability by developing a more user-friendly and acceptable nasal spray. Our research into the role of training in the effectiveness of THN has underpinned changes in policies and practices in the UK, the US and globally, and increased the availability of naloxone, saving lives worldwide in 23 countries which now have documented THN programmes **[A]**.

King's research drove and informed commercial development of naloxone in the form of a nasal spray. Based on the strength of King's research (**5**), Mundipharma decided to test and develop nasal spray forms of naloxone. King's researchers contributed to the design of trials and collaborative research (**7**) that formed the evidence base for the regulatory approval of the resulting product, Nyxoid, across Europe and Australia. Nyxoid is progressively being introduced into public policy and clinical practice **[B1, B2, B3]**.

King's research led to UK policies recommending THN, and its implementation.
UK Government approval for THN was confirmed in 2015, with nasal naloxone added in 2019 **[C1]**, referencing for advice an open letter describing King's THN research on the necessity for training **[C2]**. The development of Public Health England (PHE) clinical national guidelines (AKA the Orange Guidelines), featuring King's research on THN (**5**) and chaired by King's researcher Strang, influenced Government decision making **[C3]**. In England 95% of local authorities now provide THN and 40,033 THN kits were dispensed in community settings in 2017/18 **[C4]**. In Northern Ireland the Public Health Agency's THN programme supplied 1,332 kits in 2018/19 **[C5]**. In Scotland, 8,379 THN kits were distributed in the year 2017/18 **[C6]**. In Wales 4,120 THN kits were issued in 2017/2018 **[C7]**. Based on King's research, pilot schemes were launched in 2020 to train police officers to administer naloxone in North Wales, Durham and West Midlands. The North Wales Police and Crime Commissioner said: *"The research carried out by King's College London on the effectiveness of naloxone in saving lives of those experiencing an overdose contributed to the vision of piloting officers carrying naloxone in North Wales."* Police officers on the pilot have already saved lives **[C8]**. The chair of the expert sub-committee of the Advisory Council on the Misuse of Drugs which is examining THN, and makes recommendations to the UK government, cites King's research (**3,4**) as shaping its understanding of the potential for further public benefit from the expansion of THN in the UK **[C5]**.

King's research informed US policy on THN for overdoses of prescription opioids.
In 2017 alone, an estimated 47,600 people died from opioid overdose in the US. King's researchers have been influential in the development of US policy to address this widespread problem. Professor Keith Humphreys, previously Senior Policy Advisor for the Obama administration, included naloxone in the 2010 US Drug Strategy **[D1]**, which paved the way for a host of subsequent policies widening the availability of THN. For example, in 2016 the US Surgeon General endorsed THN **[D2, D1]**, and in 2018, Congress passed the SUPPORT Act (Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act) **[D3, D1]**. In 2016 Humphreys *'used Professor Strang's work extensively in working with Congress on the CARA Act (Comprehensive Addiction and Recovery Act 2016), which expanded naloxone even further, allocating over $180 million to provide naloxone to individuals taking prescribed or illicit opioids and their families'* **[D1, D4]**. Nasal and injectable THN kits are now provided to PWUOs in the US, and co-prescribed with opioids for medical treatment. King's research has resulted in naloxone being used by police officers, homeless shelter workers, firefighters, prison staff, as well as opioid users and their families. Naloxone prescriptions more than doubled from 270,000 to 576,000 from 2017 to 2018 **[D5]**, and in 2019, 94% of Syringe Service Programs in the US implemented overdose education and naloxone distribution compared to 55% in 2013 **[D6]**.

King's research influenced global THN policies. King's researchers advocated for and contributed to the first-ever guidelines from the WHO on the 'Community Management of Opioid Overdose' (2014) **[E1, E2]**. The guidelines draw heavily on King's research (**2,3**) to call for increased availability of THN and training. In 2016 King's research underpinned a declaration from the United Nations General Assembly calling for national policies to include THN **[E3, E2]**, leading to widespread uptake **[A]**. King's research directly contributed to the UNODC Stop

Overdose Safely 90-90-90 S-O-S initiative **[E4,E2]**. King's researchers also co-designed and co-delivered UNODC strategy for the implementation and evaluation of THN provision at national and regional levels in countries that either produce heroin or are located along the trade routes for heroin to Western Europe. Anja Busse, UNODC, says King's researchers: *"have been invaluable contributors to UNODC's development of training materials, international training events in countries including Kyrgyzstan, Kazakhstan, Tajikistan, and regional training events in Iran which was also for Afghanistan and neighbouring countries… [these] underpin the development of Take-Home Naloxone provision in these countries which did not formerly have expertise in the public benefit of Take Home Naloxone"* **[E2]**. As of August 2020, this initiative has delivered training to 16,000 potential witnesses of opioid overdose in Kazahkstan, Kyrgystan, Tajikstan and Ukraine and provided THN kits to 40,000 people as part of a study **[E5]**.

The European Monitoring Centre for Drugs and Drug Addiction provides the European Union with evidence on European drug problems. King's researchers authored its 2016 guide on best practices on THN **[E6]**, where King's research is featured (**2,3,5**), and the King's Bradford Hill review (**1**) informs the Centre's guidance on naloxone **[E7]**. King's research has impacted policy decisions nationally in Europe. For example, King's research supported the National Centre for Addiction Research in Norway in advocating for THN provision, leading to the launch in 2014 of a National Overdose Prevention Strategy distributing about 8,000 THN kits in the first four years. A 95% survival rate was recorded in about 600 uses of THN on overdose victims in the first 2.5 years **[E8]**.

Take-Home Naloxone saves lives. King's research continues to demonstrate the effectiveness and feasibility of THN as a public health intervention, whilst advocating for increased provision and training to ensure that THN is available in the community to save lives. In Northern Ireland alone THN was administered 240 times in 2018-19 and was successful in reversing an opioid overdose in over 90% of cases. As Michael Owen, Lead for Drugs and Alcohol at Northern Ireland's Public Health Agency said: *"each overdose reversal is an occasion when a person could have died, but didn't"* **[F1]**. First-hand accounts from those who have been trained to use THN demonstrate its powerful impact. A PWUO who had saved the life of his friend with THN said *"I've administered naloxone once to a friend of mine who was minutes away from death…gasping for air and barely breathing…and within a minute she was sitting up and talking. It was that simple and that quick"* **[F2].** The development of the more acceptable nasal spray coupled with THN training have together empowered a broader range of witnesses to receive training and administer THN. The British Red Cross deliver such training to PWUO, their friends and families. One of their delegates said *"just knowing and saving someone's life, it's better than any drug in the world you know, any drug in the world"* **[F3]**. These changes in THN availability and use could not have happened without King's research identifying the barriers to use, improving the product, providing the evidence to increase uptake, and influencing policy across the world.

5. Sources to corroborate the impact

[A] Harm Reduction International 2019 global audit

[B] Sources corroborating that King's research underpinned the commercial development of a nasal spray form of naloxone

B1 Testimony from Mundipharma.
B2 European Medicines Agency regulatory approval of Nyxoid 2017
B3 Nyxoid leaflet Australia.

[C] Sources corroborating the influence of King's research on UK guidelines and policy on Take Home Naloxone

C1 UK government statement on widening the availability of naloxone 2019
C2 Open letter from Professor Sir John Strang 2015
C3 Drug Misuse and Dependence: UK Guidelines on Clinical Management, AKA 'The Orange Guidelines' 2017
C4 Carre, Z. & Ali, A. (2019) Finding a Needle in a Haystack: Take-Home Naloxone in England 2017/18, London: Release.

C5 Testimonial from Anne Campbell, Chair of expert subcommittee on the Advisory Council for the Misuse of Drugs, containing THN statistics for Northern Ireland
C6 National Naloxone Programme Scotland: Monitoring Report 2017-18
C7 Wales Harm Reduction Database Wales: Take Home Naloxone 2018
C8 Testimonial Arfon Jones, North Wales Police and Crime Commissioner

[D] Sources evidencing the role of King's research in the use of Take-Home Naloxone in the United States

D1 Testimonial from Professor Keith Humphreys, Senior Policy Advisor to President Obama
D2 US Surgeon General statement about THN 2018
D3 SUPPORT Act (Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act) 2018
D4 CARA Act (Comprehensive Addiction and Recovery Act) 2016
D5 US Prescription current statistics from Centers for Disease Control and Prevention (CDC) website
D6 US Syringe Service Programs 2019 statistics from Centers for Disease Control and Prevention (CDC)

[E] Sources corroborating that King's research led to Take-Home Naloxone initiatives and policies globally

E1. WHO Community Management of Opioid Overdose Guideline 2014
E2 Testimonial from Anja Busse of the United Nations Office on Drugs and Crime
E3 United Nations General Assembly Special Session on the World Drug Problem 2016
E4 WHO-UNODC S-O-S (Stop Overdose Safely) 90-90-90 initiative 2016
E5 UNODC countries involved in the heroin trade 2020
E6 EMDCA Preventing opioid overdose deaths with Take Home Naloxone Guideline 2016
E7 EMCDDA countries in Europe using Take Home Naloxone
E8 Testimony from Professor Thomas Clausen Director of Norway National Addiction Centre

[F] Sources from first person stories or case studies demonstrating how THN saves lives

F1 Michael Owen, Northern Ireland Public Health Agency webpage 2020
F2 King's Spotlight Video
F2 Red Cross Community Based first aid film 'Saving Lives, Changing Lives'