Institution: University of Edinburgh		
Unit of Assessment: 1		
Title of case study: D: De-medicalisation of contraception to improve access and prevent unintended pregnancies		
Period when the underpinning research was undertaken: 2006 – 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:**
Sharon Cameron Anna Glasier	Honorary Professor Honorary Professor	2006 – present 2004 – 2009
Period when the claimed impact occurred: August 2013 – December 2020		
Is this case study continued from a case study submitted in 2014? N, although UPA licencing on a prescription-only basis was reported in REF2014/1/S.		

1. Summary of the impact

Underpinning Research: University of Edinburgh (UoE) researchers have investigated 2 strategies to simplify and improve access to effective methods of contraception so as to give women a better chance to prevent unintended pregnancy: first, long-acting reversible methods of contraception (LARCs) and second, effective methods of emergency contraception (EC). They developed strategies to improve access to LARC, including self-administration of the LARC Progestogen-only injectable and providing LARC immediately following abortion, and demonstrated that a new oral EC, ulipristal acetate (UPA), had a longer timeframe of action than the existing EC levonorgestrel.

Significance and Reach of Impact: Based on UoE research, in 2015 the Medicines and Healthcare products Regulatory Agency approved the Progestogen-only injectable for home self-administration. UoE research has informed 11 national and international guidelines, including the UK's National Institute for Health and Care Excellence and World Health Organization, which have since 2014 recommended improved access to the most effective contraceptive methods.

In 2015, the European Commission made UPA available without prescription from the pharmacy in 23 European Union countries, based on UoE data. Between 2014 and 2019, over-the-counter EC sales increased from 4,996,000 to 7,443,000 packs, and the proportion of UPA sales relative to levonorgestrel increased from 8.6% to 35.4%. Sales of the Progestogen-only injectable in England increased from under 300 per month before home-administration was approved, to over 5,000 per month in July 2020.

2. Underpinning research

The Challenge: Difficulties in timely access to the most effective contraception leads to lower uptake and more unintended pregnancies

Some 1 in 3 women in the UK are estimated to have an abortion at some point in their reproductive lives, translating to approximately 200,000 abortions in the UK every year. Unintended pregnancy is distressing for women and constitutes a serious public health problem estimated to cost the NHS over GBP1,000,000,000 in 2012.

Many unintended pregnancies occur despite women using contraception at the time of conception, as methods such as condoms and pills are often used inconsistently or incorrectly, and are therefore less reliable than LARCs. Greater uptake of the most effective LARC methods (injectable, implant and intrauterine methods) could prevent many more unintended pregnancies. Since 2006, UoE researchers and clinicians Cameron and Glasier have built a strong evidence base for 1) simplifying access to the most effective LARC methods and 2) improving access to 'back-up' EC when a contraceptive method was not used or has failed.

Regular Contraception: Self-administration of a Progestogen-only injectable is effective and acceptable to women

The Progestogen-only injectable is a contraceptive method that formerly needed to be injected intramuscularly every 3 months by a healthcare professional. UoE researchers demonstrated in a pivotal study that women could correctly self-administer a subcutaneous preparation themselves, and at the appropriate 3-monthly interval, for up to 1 year. Home-administration showed similar effectiveness, continuation rates and satisfaction as clinician-administered preparations [3.1].

Emergency contraception: Trial evidence for an effective drug with a longer time window for administration

When regular contraception has failed or was not used, EC can prevent an unintended pregnancy. A meta-analysis that included a UoE-led international randomised controlled trial (RCT) [3.2] demonstrated the superior effectiveness of a new oral EC — ulipristal acetate (UPA) — over the existing oral EC levonorgestrel, including a longer effective time window of up to 120 hours after unprotected sex, compared with levonorgestrel's 72 hours. This led to the marketing approval in 2010 of UPA as an EC method in the European Union (EU) and United States (REF2014/1/S). Since REF2014, the UoE group has demonstrated that all EC was less effective in women with higher body mass, but that this effect was less pronounced for UPA than for levonorgestrel [3.3].

Pharmacy access to regular contraception following EC leads to higher uptake of effective contraception

Unless women start effective regular contraception after using EC, they remain at risk of unintended pregnancy. Most women in the UK obtain EC from community pharmacies, which are unable to provide regular contraception apart from condoms. UoE research found in a cluster RCT (n=636) in 29 pharmacies in 3 UK cities that pharmacy provision of a 'bridging' 3-month oral contraceptive pill along with EC, plus an invitation to attend a sexual and reproductive health clinic, resulted in 20% more women using effective contraception 1 month after the end of the supply of the 'bridging' pill, compared with a control group where only contraceptive advice was given with EC [3.4]. Importantly, significantly fewer (n=20) women in the intervention group required to use EC again during the 4-month follow-up period, compared with the control group (n=37).

Post-abortion contraception: Delivery of abortion services in a community setting and immediate uptake of the LARCs reduce further unintended pregnancies

The UoE group's pioneering health services research demonstrated that abortion services can safely be shifted from hospitals to community specialist contraceptive healthcare settings. Moreover, provision of abortion services in a community setting was associated with improved uptake of the most effective LARC methods, compared with when care was delivered from a hospital setting. Importantly, the group also showed that women who chose a LARC method have 18–20 fold lower risk of a further abortion within the next 2 years, compared with those choosing oral contraceptive pills [3.5].

Together with Swedish colleagues, UoE researchers also demonstrated in an RCT with 551 women that immediate provision of a LARC, in this case the contraceptive implant, at the time of medical abortion rather than at a follow-up visit, was safe and effective and resulted in higher uptake of this method and significantly fewer subsequent unintended pregnancies within the next 6 months (0.8% compared with 3.8%) [3.6]. Women also preferred immediate rather than delayed provision of the implant.

3. References to the research

[3.1] Cameron ST, Glasier A, Johnstone A. Pilot study of home self-administration of subcutaneous depo-medroxyprogesterone acetate for contraception. Contraception 2012; 85: 458–464 doi: 10.1016/j.contraception.2011.10.002

[3.2] Glasier AF, Cameron ST, Fine PM, Logan SJS, Casale W, Van Horn J, Sogor L, Blithe DL, Scherrer B, Mathe H, Jaspart A, Ulmann A, Gainer E. Ulipristal acetate versus levonorgestrel for emergency contraception: a randomised non-inferiority trial and meta-analysis Lancet 2010; 375:555 doi: 10.1016/S0140-6736(10)60101-8

[3.3] Glasier A, Cameron ST, Blithe D, Scherrer B, Mathe H, Levy D, Gainer E, Ulmann A. Can we identify women at risk of pregnancy despite using emergency contraception? Data from randomized trials of ulipristal acetate and levonorgestrel. Contraception 2011; 84 (4) 363-367 doi: 10.1016/j.contraception.2011.02.009

[3.4] Cameron ST, Glasier A, McDaid L, Radley A, Baraitser P, Stephenson J, Gilson R, Battison C, Cowle K, Forrest M, Goulao B, Johnstone A, Morelli A, Patterson S, McDonald A, Vadiveloo T, Norrie J. Use of effective contraception following provision of the progestogen-only pill for women presenting to community pharmacies for emergency contraception (Bridge-It): a pragmatic cluster-randomised crossover trial. Lancet 2020; 396(10262), 1585-1594. doi: 10.1016/S0140-6736(20)31785-2

[3.5] Cameron ST, Glasier A, Chen ZE, Johnstone A, Dunlop C, Heller R. Effect of contraception provided at termination of pregnancy and incidence of subsequent termination of pregnancy. BJOG 2012; 119:1074-80 doi: 10.1111/j.1471-0528.2012.03407.x

[3.6] Hognert H, Kopp Kallner H, Cameron S *et al*. Immediate versus delayed insertion of an etonogestrel releasing implant at medical abortion—a randomized controlled equivalence trial. Human Reproduction 2016; 31:2484-2490. doi: 10.1093/humrep/dew238

Selected grant awards:

[3.7] National Institute for Health Research (NIHR) 'A randomised controlled trial to determine the effectiveness of bridging from emergency to regular contraception: The 'Bridge-it' study' (2017–2019). Cameron S, Norrie J, Glasier A, Radley A, McDaid L, Trussell J, Stephenson J, Barraitser P. GBP1,100,000

[3.8] Chief Scientist Office 'Integrating Abortion within a Specialist Contraceptive Service: A Qualitative Evaluation of the Experiences of Women and Health Professionals' (CZH/ 4/906). (2013–2015). Harden J, Cameron ST, Lawton, Kirkham, Glasier AG. GBP122,000

4. Details of the impact

Unintended pregnancies have adverse consequences for women's clinical, social and economic wellbeing. UoE's work promoting de-medicalised self-care interventions and simpler access to the most effective contraceptive methods and EC is in line with the World Health Organization (WHO)'s *"push towards new and greater self-efficacy, autonomy and engagement in health for self-carers and caregivers"* [5.4a] and will result in significantly fewer unintended pregnancies and subsequent abortions [3.5; 3.6].

Impact on regulatory authorities

Progestogen-only injectable for home self-administration

In 2015, the Medicines and Healthcare products Regulatory Agency (MHRA) approved the subcutaneous preparation of the Progestogen-only injectable (brand name Sayana Press) for home self-administration, citing UoE research [3.1] as 1 of 2 pieces of evidence [5.1]. Home administration is included in online NHS guidance, for example: *"You can have the Sayana Press injection in your tummy (abdomen) or thigh and would normally learn to do this yourself."* [5.2]. Women can now be taught how to self-administer and receive 12 months' supply to keep at home and inject at the scheduled time (every 3 months).

Emergency contraception UPA changed to non-prescription status

The marketing approval of UPA on a prescription-only basis was reported in REF2014. Since then, the European Medicines Agency (EMA) reviewed the clinical and biological evidence on UPA for EC and, based on the data from UoE's trial [3.2], recommended a change in its classification to non-prescription status in 2015 [5.3a]. Subsequently, the European Commission authorised the

sales of UPA without prescription in pharmacies throughout the EU in 2015. The EMA highlighted that one advantage of the UPA product 'ellaOne' over levonorgestrel was *"that ellaOne can be taken up to 120 hours after unprotected intercourse in contrast to levonorgestrel 1.5 mg"* [p.67; 5.3b]; this was based on the findings of paper [3.2].

Impact on guidelines

Progestogen-only injectable for home self-administration
In 2019, the WHO, in their first-ever consolidated guidelines on self-care interventions for sexual and reproductive health and rights, strongly recommended the self-administration of subcutaneous progestogen-only injectable [p.53; 5.4a] based on a systematic review that cited 2 UoE publications [5.4b].

UPA for EC
Since 2015, UoE research on UPA for EC has led to its recommendation for use by the WHO, the International Consortium for Emergency Contraception and the Faculty of Sexual and Reproductive Healthcare UK (FSRH) [5.5 a–f]. Notably, the UoE finding that the effectiveness of UPA was less affected by higher body mass than levonorgestrel influenced the FSRH guidelines, such that UPA is recommended as first choice over levonorgestrel, and where a woman with a higher body mass chooses levonorgestrel, a double dose is recommended [5.5d].

Post-abortion contraception
UoE studies on post-abortion contraception are extensively cited in UK and WHO guidelines on contraception following abortion [5.6]. The FSRH Guideline "Contraception After Pregnancy" (2017) cites 10 UoE publications, leading to 3 high-graded and 2 medium-graded recommendations on the provision of LARC after an abortion [5.6a]. Updated WHO guidance on medical management of abortion (2018) cites publication [3.6] as one of 4 studies underpinning new recommendations to provide contraception immediately post-abortion [5.6d].

The UK's National Institute for Health and Care Excellence (NICE) updated their Abortion Care guidelines in September 2019 [5.6b]. Section 1.15 ("Improving access to contraception") includes 2 UoE publications, including [3.6], in the evidence review [5.6c], leading to Recommendation 1.15.4 that providers should offer LARC methods of contraception at the time of surgical abortion or as soon as possible after successful medical abortion [p.20; 5.6b]. The same NICE guideline update also evaluated the cost-effectiveness of immediate versus delayed administration of LARC following a medical abortion, and concluded that access to immediate provision of contraception was cheaper by up to GBP82 per patient [5.6c].

Impact on health services and women's health and welfare
Access to EC, including UPA, had previously required a doctor's prescription in Europe; thus, the change to non-prescription status in 2015 [5.3] based on UoE trial evidence represents a step-change in women's access to EC, and greatly helps to reduce their risk of unintended pregnancy. This benefit to women's health was a key reason behind EMA's decision to approve UPA for over-the-counter sales: *"[It is in] women's and public health interest that women requesting EC after unprotected intercourse can be promptly offered ulipristal acetate 30mg to get the best chance of preventing an unwanted pregnancy; only pharmacy access will ensure that every woman can access it as early as possible after unprotected intercourse."* [p.25; 5.3b].

By November 2015, UPA was available without prescription in 23 EU countries [5.7]. This led to an overall increase in over-the-counter sales of all EC from 4,996,000 packs sold in 2014 to 7,443,000 in 2019. Over the same period, the proportion of UPA sales relative to levonorgestrel increased from 8.6% in 2014 to 35.4% in 2019 [5.8].

Sales of Progesterone-only injectable (Sayana Press) since 2015
Since the MHRA approved the progestogen-only injectable for home administration, sales of the product Sayana Press have increased across England from 287 prescriptions (generating

GBP1,941 income) per month in August 2015, to 5,088 prescriptions (generating GBP49,062 income) per month in July 2020 [5.9].

5. Sources to corroborate the impact

[5.1] MHRA approval of self-administration of Progestogen-only injectable:
a. MHRA Public Assessment Report 2015 – Self-administration of Sayana Press (Progestogen-only injectable); citing "Cameron study GA67816", which is [3.1]
b. The Summary of Product Characteristics, stating self-administration in the label (Section 4.2)

[5.2] NHS website about Progestogen-only injectable (includes self-administration)

[5.3] EMA decision on over-the-counter UPA availability:
a. Recommendation (21st Nov 2014)
b. Assessment Report (4th Dec 2014) ([3.2] was one of only 3 studies (and the only phase III trial) used as evidence in the assessment of the clinical efficacy aspect of UPA; "Phase III Trial HRA2914-513" and "meta-analysis HRA2914-541" in Section 2.3 (p.9-12) on Clinical Efficacy both refer to [3.2])
c. Final Study Report on [3.2] submitted to funders HRA Pharma, showing that HRA2914 was the name given to UPA and the trial was formally titled HRA2914-513.

[5.4] Guidelines recommending self-administration of Progestogen-only injectable:
a. WHO 2019 Consolidated Guideline on Self-Care Interventions for Health Sexual and Reproductive Health and Rights; quote on p. xi
b. Kennedy CE, Yeh PT, Gaffield ML, et al Self-administration of injectable contraception: a systematic review and meta-analysis BMJ Global Health 2019;4:e001350. doi: 10.1136/bmjgh-2018-001350

[5.5] Guidelines recommending UPA as emergency contraception and including UoE research regarding weight and contraceptive timings:
a. WHO 2015 Medical eligibility for contraception (2 references)
b. WHO 2016 Practice recommendations for contraceptive use (2 UoE references)
c. FSRH 2016 UK medical eligibility for contraception (chair: Sharon Cameron)
d. FSRH 2017 Emergency contraception (10 UoE references)
e. FSRH 2017 Quick starting contraception (4 UoE references)
f. International Consortium for Emergency Contraception 2018: Emergency contraceptive pills. Medical and Service Delivery Guidance 4th edition (3 UoE references)

[5.6] Clinical guidelines and policies recommending improved access to contraception after abortion and better post-abortion management based on UoE research:
a. FSRH 2017 Contraception after pregnancy (10 UoE references leading to 3 high-graded and 2 medium-graded recommendations)
b. NICE 2019 Abortion Care Guidelines (2 UoE references included in expert review P [5.6c])
c. Expert Review P (NICE 2019) Contraception after termination of pregnancy, Appendix J; Tables 20 and 21
d. WHO 2018 Medical management of abortion (2 UoE references leading to 2 new recommendations; p.32–33)

[5.7] European Consortium for Emergency Contraception: Country uptake of UPA in the EU

[5.8] HRA Pharma Data to evidence over-the-counter sales of emergency contraception in the European Union (2014–2019) - a) Raw data b) Figures

[5.9] Sales of Sayana Press in England August 2015-August 2020. OpenPrescribing.net, EBM DataLab, University of Oxford, 2020 Complete dataset available here.