LNG may still be the most cost-effective oral emergency contraceptive method: authors' response

We would like to respond to the comments of Pittrof and colleagues[1] regarding our paper 'Is it worth paying more for emergency contraception?' The cost effectiveness of ulipristal acetate versus levonorgestrel 1.5 mg'.[2]

1. Pittrof *et al.* claim incorrectly that the two comparative randomised controlled trials (RCTs) of ulipristal acetate (UPA) and levonorgestrel (LNG) were underpowered. Both studies were designed as non-inferiority studies (to show that UPA was no less effective than LNG) and were adequately powered to do this.[3 4]
2. Pittrof *et al.* do not accept that a meta-analysis using different drug regimens in the RCTs is acceptable. The scientific peer reviewers/statisticians of the *Lancet* considered this meta-analysis to be appropriate, as did National and European regulatory authorities including the Scottish Medicines Consortium and the European Medicines Authority. A detailed explanation of the rationale for the drug regimes used and their comparability is contained within the original *Lancet* article.[4]
3. Pittrof *et al.* postulate that UPA for emergency contraception (EC) could predispose to placenta praevia. The scientific rationale behind this is flawed and there is no reported association between use of another progesterone receptor modulator (mifepristone), which has been widely used for many years now for EC in China, and placenta praevia.
4. Pittrof *et al.* raise concern about potential effects of UPA on the endometrium around the time of implantation. However, recent studies have shown that the effect on the endometrium is dose dependent.[5] When a single dose of UPA or placebo was given just after ovulation, a delay in endometrial maturation (histological dating) was only observed at the highest dose (100 mg) while the effect of lower doses of UPA equivalent to the 30 mg micronised dose used for EC were similar to that of placebo.[5]
5. Pittrof *et al.* claim that use of UPA for EC could result in abnormal trophoblast invasion and consequent adverse outcomes in pregnancy. Although over 4000 women have been exposed to UPA in clinical trials to date, the number of women who have become pregnant after taking it and have chosen to continue with the pregnancy has been small in number. In the Glasier *et al.* study, most women in whom EC (UPA or LNG) failed, opted to have a termination.[4] While we know that the spontaneous abortion rate was no different between UPA- and LNG-treated women, and that the small number of births reported after UPA exposure have been unaffected,[3 4] clearly UPA is a new drug and so it is entirely appropriate that a registry has been created with the European Medicines Agency to obtain more information.
6. Pittrof *et al.* claim that obstetricians may undertake more ultrasound surveillance of any pregnancy that has been exposed to a new drug with a 'black triangle' label from the Medicines and Healthcare products Regulatory Agency (intensively monitored drug). In such circumstances, a fetal anomaly scan would be the most appropriate form of obstetric monitoring and antenatal patients in the UK are currently offered a fetal anomaly scan (included in our cost analysis). Clearly however it is impossible to account for any additional tests that individual obstetricians may, or may not, institute in individual cases.
7. We agree that increased used of intrauterine devices (IUDs) should be promoted as the most effective method of EC. Nevertheless, IUDs are not currently a popular choice with women,[6 7] they require skilled staff to insert and have a risk (albeit low) of important complications such as uterine perforation and infection. Consequently, women do still require an effective orally active alternative. Furthermore, since UPA is effective up to 120 hours after unprotected sex, women who may not have bothered to present for EC because they thought they were too late can now avail themselves of this method.
8. Pittrof *et al.* dismiss the use of economic analysis for contraception as a commissioning tool, but at a population level, economic evaluation studies for contraception are important, because in spite of prioritisation of sexual health at national policy level in recent years and additional investment to support this, it is clear that there are not unlimited resources for the National Health Service (NHS). Furthermore, in many parts of the country, women are continuing to receive a less effective oral method of EC than UPA (i.e. LNG) based on the cost of the drugs themselves. Although population studies have failed to show an effect of EC on rates of unintended pregnancy, EC will

prevent pregnancies for individual women.

9. Finally, Pittrof *et al.* have failed to appreciate that women take EC because they wish to avoid a pregnancy. For providers who have their patients' interests at heart, a more effective EC is highly desirable, and discussing the next steps in managing an unwanted pregnancy after a less effective method of EC has failed is distressing for both parties. The finding in the meta-analysis that UPA was more effective than LNG is not a surprise given the clear trend in both RCTs of higher efficacy with UPA. Furthermore, the higher efficacy is supported by the demonstration that UPA is a more potent inhibitor of ovulation, at a time in the cycle when the likelihood of pregnancy is greatest.[8]

   Women deserve the most effective EC. If women who seek oral EC are denied UPA on 'unscientific grounds' and subsequently become pregnant then this could lead to further costs, namely the costs of litigation.

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Competing interests Ramon Schmid is employed by HRA Pharma, the manufacturer of ulipristal acetate.

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