**Key Features and Requirements for your decision model**

(Adapted from CHEERS checklist)

| **Section/Item** | **No** | **Description** | **Details about your study (if applicable)** |
| --- | --- | --- | --- |
| Background and objectives | 1a | Define the study question and its relevance for health policy or practice decisions. | **Objective-** To quantify the pharmacoeconomic impact of drug-drug interactions with hormonal contraceptive agents examining the cost of unintended pregnancy and side effects.  **Relevance for practice decisions-** Numerous pharmacoeconomic evaluations have unequivocally established the cost-effectiveness of contraceptive usage as compared to no contraceptive use from a payer and a societal perspective in different country settings. Among all the different reversible contraceptive options available, hormonal contraceptives in particular have been shown to be highly cost-effective due to their high efficacy and effectiveness. Considering hormonal contraceptives, long-acting reversible contraceptives (Levonorgestrel intrauterine device, Etonorgestrel implants and copper intrauterine device) are the most cost-effective as their efficacy does not depend upon user compliance. However, their uptake has been low. Around 25% of women who use contraceptives (or 9.5 million women in the USA) rely on the oral contraceptive pill due to its convenience. Contraceptive failure on the pill is common due to non-compliance which reduces its effectiveness. Even considering full compliance, unintended pregnancies are possible in women using oral contraceptives due to contraceptive failure resulting from drug-drug interactions.  Certain interacting co-medications can reduce the concentration of the pill in the body (due to increased metabolism) and result in unintended pregnancies, while other co-medications can result in adverse events, most notably venous thromboembolism (due to inhibition of contraceptive metabolism).  Therefore, to estimate the magnitude of this problem, we would like to use a modelling framework to quantify the cost implications of drug-drug interactions with hormonal contraceptive agents.  **Relevance for health policy-** Currently, the FDA uses class-labelling based on information known about estrogens/ progestins in the drug-interaction section for contraceptive labels. There is also push in various states to increase contraceptive access by granting OTC use or pharmacist-based prescribing for oral contraceptives to women.  Around 12% of women of reproductive age in USA use 3 or more prescription drugs which could contribute to drug-drug interactions. Currently, none of the economic evaluations address the economic impact of DDIs on HCAs. |
| 1b | Are there any decision models out there already answering your research question? | There are various models which address the question of cost effectiveness of contraceptives. However, none of them have considered the impact of DDIs. This is the gap in the literature that we are looking to bridge.  We developed a registry comprising of all economic evaluations conducted on hormonal contraceptives for contraception as the outcome. The registry had 64 articles with 30 of the studies from USA. We have collected information on all the economic models developed on hormonal contraceptives.  Briefly, among the Markov models in the registry, most of these models consider a three-state Markov model, where all women begin in the “Initial contraceptive method” state and remain in that state unless they experience a contraception failure, and thus enter the “Unintended Pregnancy” state or choose to discontinue the method and enter a “Subsequent method” state. Women can continue to be in the “Subsequent method” state until they similarly, experience a method failure, at which time they again enter the “Unintended Pregnancy” state.  In order to obtain a purer estimation of the impact of DDIs, we are considering a modification to the above approach by not considering “discontinuation” of contraceptive. Instead in our model, a woman continues to be on the pill unless she experiences a method failure OR an adverse event due to a DDI. |
| Target population and subgroups | 2 | Describe characteristics of the base case population. | The target population is a cohort of healthy or “at risk” women aged 15-44 years (reproductive age) using hormonal contraceptive pills with an intention to avoid pregnancy. By “at risk” we mean, women who have co-morbid conditions that require using interacting co-medications along with hormonal contraceptive pills. (For example, anti-epileptics, anti-retrovirals) etc. |
| Setting and location | 3 | State to which setting and location does this decision model apply. | Currently, the model applies to USA from a primary/ secondary care setting. Most women might receive their contraceptives from their primary care physicians. However, given that our clinical question pertains to drug-drug interactions, decisions regarding prescribing co-medications might come from a secondary care (specialist) setting as well. |
| Study perspective | 4 | Decide on the perspective of the study and relate this to the costs being evaluated. | Our perspective is that of a payer perspective. We will consider only direct medical costs. We have compiled the costs from all economic evaluations on hormonal contraceptives conducted in USA. Therefore, the costs include third-party payer as well as public-payer perspective. |
| Comparators | 5 | Which interventions or strategies are being compared? | The three strategies being compared are-   1. Women on oral contraceptives alone 2. Women on oral contraceptives PLUS enzyme inducers (Here, we consider a generic hypothetical enzyme inducer drug, which likely leads to greater unintended pregnancy) 3. Women on oral contraceptives PLUS enzyme inhibitor (Here, we consider a generic hypothetical enzyme inhibitor drug, which likely leads to greater adverse events) |
| Model type | 6 | What type of decision model you think you need? How important is the effect of time in the question you are trying to answer? | We are thinking of using a Markov model, as we aim to quantify the additional costs/ outcomes between the three strategies at different time points.  We could have a static model assuming same “inherent average fertility” in women (ie, fertility remains same in all age groups). However, we could also choose to account for changing fertility of women (declining as they age) as an additional factor (For example, in 5-year increments 15-19 years, 20-24 years…) therefore, time maybe an important aspect to consider in our model |
| Model structure | 7 | What are the most important health states / events / pathways that will be in your model | All women begin in the “Pill only” state and remain in that state unless they experience an unintended pregnancy (“Unintended pregnancy”) state or an adverse event (“Adverse event”) state. From the “Unintended pregnancy” state, women could have four outcomes “Birth”, “Induced abortion”, “Spontaneous abortion” and “Ectopic pregnancy”. From the “Adverse event” state women could experience “Venous thromboembolism”, “Myocardial infarction”, “Stroke”, “Irregular bleeding” or “Amenorrhea”.  In the other strategies, instead of women being in the “Pill only”, they start at “Pill + enzyme inducer” or “Pill + enzyme inhibitor” state |
| Time horizon | 8 | Choose a time horizon(s) over which costs and consequences are being evaluated. | Since we are considering a hypothetical interacting drug, we wanted to consider different time horizons to account for acute as well as chronic drugs.  Therefore,   1. 1 year (for chronic medications) 2. 5 years (for drugs to be taken life-long) |
| Discount rate | 9 | Report the choice of discount rate used for costs and outcomes and say why. | We’ll be using a discount rate range of 3-6%. Our pharmacoeconomic registry has shown most economic evaluations conducted on hormonal contraceptives have used this discount rate range. |
| Choice of health outcomes | 10 | Determine which health outcomes will be used as the measure(s) of benefit in the evaluation (e.g. LYs, QALYs). | 1. Number of unintended pregnancies (each unintended pregnancy outcome, for eg, birth, induced abortion…) 2. Number of adverse events (each adverse event outcome, for eg, VTE, MI etc) 3. QALYs (in each of the interventions) |
| Measurement of effectiveness | 11 | What type of data you have available to estimate the effectiveness (RCT, expert opinion etc)? Will evidence synthesis be used? | Effectiveness measure (Pregnancy rate/ Pearl Index)   1. Oral contraceptive alone strategy-The effectiveness data (failure rate of contraception under perfect use) comes from RCTs. This information is mostly in the form of a Pearl Index (number of contraceptive failures per 100 women-years of exposure) 2. Oral contraceptive PLUS interacting medication strategy- We have Pearl Indices which were modelled using model based meta-analysis   Safety measure (adverse events)- Venous thromboembolism, myocardial infarction, stroke, irregular bleeding and amenorrhea |
| Measurement and valuation of preference based outcomes | 12 | If you are doing a cost-utility analysis do you have HRQoL data? | Yes HRQoL utilities are available for the various outcomes |
| Estimating resources and costs | 13 | Describe data sources used to estimate costs/resource use associated with model health states | We developed a registry comprising of all economic evaluations conducted on hormonal contraceptives for contraception as the outcome. The registry had 64 articles with 30 of the studies from USA. The cost data was summarized from those studies. The costs were inflated to 2020 using the Medical care component of the consumer price index.  1. For total costs of using oral contraceptives (Cost of oral contraceptive + cost of office visit (consultation)), the total costs were calculated, inflated to 2020 using Medical Care component of CPI  2. For costs of pregnancy outcomes, similarly, costs from the individual studies were inflated to 2020  Median, minimum and maximum were then calculated from those values. |
| Assumptions | 14 | Describe assumptions underlying your model | 1. The analysis applies applied only to women aged 15-44 years who are sexually active and are not looking at becoming pregnant during the time horizon of the analysis. Therefore, all pregnancies occurring during the time horizon due to method failure are assumed to be unintended. 2. All women in the “Pill only” strategy are assumed to be healthy with no pre-existing medical condition. Women in the “Pill + enzyme inducer” or “Pill + enzyme inhibitor” strategy are assumed to have a pre-existing medical condition that necessitates a co-medication that interacts with the oral contraceptive pill 3. We assume that women do not switch between contraceptive methods during the time horizon of the study. 4. Women do not discontinue the initial method, ie, Pill, Pill + Enzyme inducer or Pill + Enzyme Inhibitor (They continue on pill unless they experience an unintended pregnancy or adverse event, after which they discontinue). Therefore, we don’t account for a “subsequent method” state (as we would then have to consider the subsequent method failure, which may not give us a pure estimation of our study question) 5. Terminal outcomes “Birth”, “Induced abortion”, “Spontaneous abortion”, “Ectopic pregnancy”, “Venous thromboembolism”, “Myocardial infarction”, “Stroke”, “Irregular bleeding”, “Amenorrhea” are assumed to be absorbing states. 6. We assume 100% adherence to therapy. (To ensure that contraceptive failure is not due to “user failure or non-compliance of contraceptives” and only due to “method failure” due to DDIs.) 7. Contraceptive failure occur at midpoint of cycle 8. Not all unintended pregnancies are truly unwanted, some might be simply “mistimed”. Around 60% will be assumed to be mistimed and costs of “birth” will be discounted to account for this. Mistimed births will be assumed to occur two years later. 9. Effectiveness (or failure rate) for first year will be the same in subsequent years 10. Pearl Index is assumed to be the annual probability of contraceptive failure 11. A birth is assumed to last 10 months, induced abortion 2 months, spontaneous abortion 3.5 months and ectopic pregnancy 1.5 months 12. Menopause is assumed to occur at age 45 after which there is a zero chance of pregnancy 13. A woman could get pregnant only once per year 14. Probabilities of adverse events used the following formula – P(ADE/exposed)= RR \* P(ADE/unexposed) where P(ADE/unexposed) was assumed to be the incidence # of events/ # of person-years 15. The cost of the OC+ enzyme inducer and OC + enzyme inhibitor was assumed. |