The Population Council confronts critical health and development issues—from stopping the spread of HIV to improving reproductive health and ensuring that young people lead full and productive lives. Through biomedical, social science, and public health research in 50 countries, we work with our partners to deliver solutions that lead to more effective policies, programs, and technologies that improve lives around the world. Established in 1952 and headquartered in New York, the Council is a nongovernmental, nonprofit organization governed by an international board of trustees.

Population Council
1 Dag Hammarskjold Plaza
New York, NY 10017
USA
Tel: +1 212 339 0500
Fax: +1 212 755 6052
email: pubinfo@popcouncil.org

popcouncil.org


© 2019 The Population Council, Inc.
# Table of Contents

Acronyms ...............................................................................................................................................................iv
Introduction ........................................................................................................................................................................1
Achievements ......................................................................................................................................................................2
  Result 1: Development and Approval of SA/EE IUS .................................................................................................2
  Result 2: Expand Availability and Accessibility to the PVR ......................................................................................4
Approaches and Tools for Market Entry ........................................................................................................................7
Technical Assistance .........................................................................................................................................................7
Partnership and Collaboration ......................................................................................................................................8
Knowledge Outputs .........................................................................................................................................................9
Leveraged Opportunities ...............................................................................................................................................10
Transition Plan After Project Period ..........................................................................................................................11
  Ring Collaborative .......................................................................................................................................................11
  Post-marketing Studies on SA/EE CVS .......................................................................................................................11
  Technology Transfer of the PVR ...............................................................................................................................11
  Planning for Introduction in Kenya, Nigeria, Senegal and India ............................................................................11
Conclusion .......................................................................................................................................................................13
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMGF</td>
<td>Bill &amp; Melinda Gates Foundation</td>
</tr>
<tr>
<td>CBR</td>
<td>Center for Biomedical Research</td>
</tr>
<tr>
<td>CIP</td>
<td>Costed Implementation Plan</td>
</tr>
<tr>
<td>CBR</td>
<td>Center for Biomedical Research</td>
</tr>
<tr>
<td>CMC</td>
<td>Chemistry, Manufacturing and Controls</td>
</tr>
<tr>
<td>CSR</td>
<td>Clinical Study Report</td>
</tr>
<tr>
<td>CVS</td>
<td>Contraceptive Vaginal System</td>
</tr>
<tr>
<td>DCGI</td>
<td>Drug Controller General of India</td>
</tr>
<tr>
<td>DCVR</td>
<td>Delivering Contraceptive Vaginal Rings</td>
</tr>
<tr>
<td>DDI</td>
<td>Drug-Drug Interaction</td>
</tr>
<tr>
<td>DMP</td>
<td>Direction de la Pharmacie et du Médicament</td>
</tr>
<tr>
<td>e-CTD</td>
<td>Electronic Common Technical Document</td>
</tr>
<tr>
<td>EE</td>
<td>Ethinyl Estradiol</td>
</tr>
<tr>
<td>EECO</td>
<td>Expanding Effective Contraceptive Options</td>
</tr>
<tr>
<td>EML</td>
<td>Essentials Medicine List</td>
</tr>
<tr>
<td>EOI</td>
<td>Expression of Interest</td>
</tr>
<tr>
<td>FDA</td>
<td>US Food and Drug Administration</td>
</tr>
<tr>
<td>FMoH</td>
<td>Federal Ministry of Health</td>
</tr>
<tr>
<td>FP</td>
<td>Family Planning</td>
</tr>
<tr>
<td>GFF</td>
<td>Global Financing Facility</td>
</tr>
<tr>
<td>HLL</td>
<td>HLL LifeCare Limited</td>
</tr>
<tr>
<td>ICMR</td>
<td>Indian Council of Medical Research</td>
</tr>
<tr>
<td>IPM</td>
<td>International Partnership for Microbicides</td>
</tr>
<tr>
<td>IUD</td>
<td>Intrauterine Device</td>
</tr>
<tr>
<td>MAH</td>
<td>Market Authorization Holder</td>
</tr>
<tr>
<td>MDP</td>
<td>Market Development plan</td>
</tr>
<tr>
<td>MEC</td>
<td>Medical Eligibility Criteria</td>
</tr>
<tr>
<td>MoH</td>
<td>Ministry of Health</td>
</tr>
<tr>
<td>NAFDAC</td>
<td>Nigeria’s National Agency for Food and Drug Administration and control</td>
</tr>
<tr>
<td>NAMPED</td>
<td>National Association of Patent and Proprietary Medicine Dealers</td>
</tr>
<tr>
<td>NDA</td>
<td>New Drug Application</td>
</tr>
<tr>
<td>NCE</td>
<td>New chemical entity</td>
</tr>
<tr>
<td>NES</td>
<td>Nestorone</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>OTC</td>
<td>Over the Counter</td>
</tr>
<tr>
<td>PDUFA</td>
<td>Prescription Drug User Fee Act</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetics</td>
</tr>
<tr>
<td>PPFP</td>
<td>Postpartum Family Planning</td>
</tr>
<tr>
<td>PQ</td>
<td>Pre-Qualification</td>
</tr>
<tr>
<td>PSI</td>
<td>Population Services International</td>
</tr>
<tr>
<td>PVR</td>
<td>Progesterone Vaginal Ring</td>
</tr>
<tr>
<td>SA</td>
<td>Segesterone Acetate</td>
</tr>
<tr>
<td>SFH</td>
<td>Society for Family Health</td>
</tr>
<tr>
<td>SOGON</td>
<td>Society of Gynaecology and Obstetrics of Nigeria</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>TA</td>
<td>Technical Assistance</td>
</tr>
<tr>
<td>TRP</td>
<td>Training Resource Package</td>
</tr>
<tr>
<td>USAID</td>
<td>United States Agency for International Development</td>
</tr>
<tr>
<td>WCG</td>
<td>WCG Cares</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
Introduction

This final project report relates to Agreement No. AID-OAA-A-13-00075, entitled Family Planning and Reproductive Health to Address Unmet Need, or simply “Delivering Contraceptive Vaginal Rings (DCVR).” The DCVR project had two main objectives: (1) Complete clinical development of the Segesterone Acetate (SA) /Ethinyl Estradiol (EE) contraceptive vaginal system (CVS) and seek regulatory approval and (2) Expand availability, accessibility and increased affordability of the Progesterone Vaginal Ring (PVR) in developing country programs for postpartum, breastfeeding women.

Vaginal contraceptives are innovations that are uniquely different from existing contraceptive formats. As woman-controlled products, vaginal contraceptives provide women with the tools for reproductive empowerment. These products allow women to exert autonomy over their use and by extension over the timing and spacing of their children. In addition, as women-controlled contraceptives, the PVR and the SA/EE CVS may provide women with discreet options when they are in relationships that are not supportive of their interest in controlling the timing and spacing of their pregnancies.

Together, the Progesterone Vaginal Ring (PVR) and the Segesterone Acetate /Ethinyl Estradiol contraceptive vaginal ring (SA/EE CVS) fill a gap in current contraceptive options. The PVR is a silicone ring containing natural progesterone similar to what the body produces. The PVR will support prolonged breastfeeding and offer an additional contraceptive option for postpartum women who are nursing. A user inserts a PVR into her vagina and keeps it in for three months of contraceptive protection. The PVR is effective as long as a woman breastfeeds four times a day and works by prolonging lactational amenorrhea. A user can use four PVRs in succession to obtain a year of protection postpartum. The PVR is currently registered and sold in ten Latin American countries.

The SA/EE CVS offers contraceptive choice for women who are no longer lactating thus providing choice in a continuum of care paradigm. The SA/EE contains a new potent progestin, segesterone acetate also known as Nestorone® (NES). Each SA/EE CVS provides a contraceptive user with thirteen months of contraceptive protection. A user inserts the CVS for 21 days and removes it for 7 days to allow for the monthly menses; after menses, the user re-inserts the same ring. An attractive feature of the SA/EE CVS is that it does not require refrigeration, an important benefit for supply chains and use in low resource settings.

Beginning with the “end in mind,” we initiated the project to introduce both products within family planning programs in countries with high levels of unmet need for family planning. DCVR was implemented in collaboration with WCG Cares; other partners included Grünenthal, QPharma, and TherapeuticsMD. Grünenthal is the manufacturer of the PVR out of its factory in Chile; QPharma manufactures the SA/EE CVS system in Malmö, Sweden, and TherapeuticsMD has the distribution rights for the SA/EE CVS in the US.

As of September 2019, $15,129,254.00 total (Core and Mission funds) had been allocated and spent on the achievement of results for the DCVR project. Of that investment, $343,254 had been raised from the USAID Mission in Nigeria for conducting introductory activities in that country. Over the life of DCVR, the Council and its partners leveraged substantial support for activities from relevant stakeholders including other governments, other donors, and NGOs. The Council exceeded its agreed-upon cost share requirement of 10%.

The project began on October 1, 2013 with a five-year project duration; subsequently, it received a one year no-cost extension concluding on September 30, 2019. The following describes the key accomplishments and highlights over the six years of the project.
Achievements

Result 1: Development and Approval of SA/EE IUS

1. Preparation of SA/EE CVS dossier

The project successfully completed two clinical studies required by the US Food and Drug Administration (FDA) after completion of the pivotal SA/EE CVS Phase 3 studies; a drug-drug interaction (DDI) study (completed in 2014) and a QT/QTc study (completed in 2015). Since the SA/EE CVS was categorized as a combination product (drug and device) the Center for Devices and Radiologic Health as well as the Center for Drug Evaluation and Research required several additional studies, including: a human centered design study to document that women understood directions for CVS use and several studies that related to the product itself, a shipping study to determine the integrity of rings and their containers under various shipping conditions, and a condom compatibility study.

The New Drug Application (NDA) team at the Center for Biomedical Research (CBR) at the Population Council, in collaboration with external consultants, prepared the files, records and documents for the non-clinical, clinical, and quality components of the NDA submission of the SA/EE CVS (in the US, to be marketed as “Annovera™”).

Our NDA included 13 clinical studies on Annovera™ alone, dozens of other studies that included segesterone acetate in another formulation (such as a gel, implant, or different ring) and 70+ non-clinical (animal or in vitro) studies to substantiate safety and efficacy. In addition, there were 75 report documents in the major Chemistry, Manufacturing and Controls (CMC) section of the NDA (Module 3) and 7 CMC summary reports in Module 2 of the NDA. The documents comprising the NDA (over 200,000 pages) were filed in the required electronic Common Technical Document (eCTD) format. The SA/EE CVS NDA was submitted successfully to the FDA for review on August 17, 2017. On August 22, 2017, the FDA confirmed that the electronic submission had been received and logged into the system without any difficulties. In October 2017, the FDA communicated to the NDA team at CBR that the NDA had been officially filed.

Following submission, the project continued to be engaged with the FDA to respond to varied questions and queries as they arose. In total there were more than 200 FDA queries that required detailed responses and the Council submitted an additional 100,000+ pages of data, description, and analysis in response to these queries.

The NDA team also prepared for an FDA audit of NDA activities and record keeping at CBR. This inspection occurred early in 2018. Following seven (7) days on site, the Inspector concluded there were no findings (no violations of the Food Drug and Cosmetic Act and related Acts). The team also prepared the 27 Phase 3 clinical sites for the possibility of an FDA audit, which included instructing all sites on accessibility and preparation of trial files, communication with FDA inspectors and accessibility of principal investigators for these inspections. We also conducted mock audits at several sites. Ultimately the FDA audited five sites (4 US sites and the Dominican Republic/Profamilia). With the exception of two observations at two sites, there were no major findings at any of the sites. The project team also engaged directly with the FDA review team and met with the team at FDA headquarters or by phone on five occasions to review items related to FDA queries and to hear from the FDA midway through their review of the NDA and as the review cycle approached the end of the Prescription Drug User Fee Act (PDUFA) timeline.

2. Approval of SA/EE CVS

The FDA approved the SA/EE CVS dossier and the SA/EE CVS was accepted for marketing in the US on August 10, 2018 under the brand name of Annovera™. With this approval, the SA/EE CVS enhances contraceptive choice for women in USAID’s priority countries since it was specially designed to account for distribution and use in low-resource
settings. In the words of Victor Crentsil, Acting Deputy Director of the Office of Drug Evaluation III in FDA’s Center for Drug Evaluation and Research “The FDA is committed to supporting innovation in women’s health and today’s approval builds on available birth control options.” The full announcement of the SA/EE CVS approval can be found at the following weblink: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm616541.htm.

An important implication of the US FDA approval indicates the possibility of Annovera’s™ procurement by large institutional buyers including USAID and UNFPA.

Annovera™ will be marketed in the US by TherapeuticsMD. At the time of writing, Annovera™ had a soft launch in the US market; we anticipate a full campaign in 2020, which will be informed by the initial learnings from the soft launch.

3. Scientific Knowledge Generated

Over the course of the project, we have generated new scientific knowledge about the SA/EE CVS and the new chemical entity (NCE) it contains—Nestorone (NES). In particular, we believe that the new knowledge generated about NES will lead to further innovations in contraceptive research and development. We highlight below select thematic areas where we have made groundbreaking contributions; there are ancillary topics on which we generated important new knowledge but are not reported here.

Safety and efficacy data: Data collected from 2,278 women participating in 12 US and international sites proved that the SA/EE contraceptive vaginal system is an effective contraceptive for 13 consecutive cycles of use. The Pearl Index, the most common measure used in clinical trials for reporting the effectiveness of a birth control method, was 2.98 (95% confidence intervals 2.13-4.06) per 100 woman-years. Kaplan-Meier analysis provided further evidence that the SA/EE CVS is 97.5% effective. Studies also confirmed that the 1 year SA/EE CVS has an acceptable safety profile. Data on safety, and the bleeding profile associated with use of the SA/EE CVS have been published in Contraception; efficacy results have been published in Lancet Global Health. Two papers on acceptability of the SA/EE CVS were published in Contraception.

QT/QTc study: Results from the human study confirmed that NES does not have a clinically relevant effect on any of the studied ECG parameters (heart rate, PR, QTcF, and QRS). An effect on placebo-corrected, change-from-baseline QTcF exceeding 10 ms could be confidently excluded. Assay sensitivity was confirmed by the moxifloxacin response. The study, therefore, constituted a clearly negative thorough QT/QTc study as defined by the ICH E14 guidance.

Drug-drug interaction (DDI) study: The DDI study investigated whether the use of an over-the-counter vaginal anti-fungal medication concomitant with the use of the SA/EE CVS will result in changes in the efficacy of the CVR or side-effects. The study tested three different formats of the anti-fungal medication--miconazole vaginal doses of 1200 mg single dose suppository, 200 mg/d for 3 days suppository, and 200 mg/d cream for 3 days. The results demonstrated that miconazole did not have a consistent effect on the release of NES and EE from the CVS. In the presence of the vaginally administered cream formulation of miconazole, 200 mg/d for 3 days was bioequivalent to no-miconazole-exposure during CVS use, whereas the 200 mg/d suppository for 3 days and the 1200 mg single dose suppository were not bioequivalent and were associated with an increased systemic level of both NES and EE. These findings suggest that the active ingredient, miconazole does not have an effect on the release of NES and EE from the CVS. In the presence of the vaginally administered cream formulation of miconazole, 200 mg/d for 3 days was bioequivalent to no-miconazole-exposure during CVS use, whereas the 200 mg/d suppository for 3 days and the 1200 mg single dose suppository were not bioequivalent and were associated with an increased systemic level of both NES and EE. These findings suggest that the active ingredient, miconazole does not have an effect on the release of NES and EE from the CVS.

Bioactivity profile of Nestorone (NES) and its metabolites: Studies that were completed during the project period provided additional information on the bioactivity profile of NES and its metabolites. These included the in vitro steroid receptor transactivation studies with progesterone and mineralocorticoid receptors and in vivo study to measure mineralocorticoid activity of NES in rodents. The in vivo studies provided further evidence that NES is much more potent in activation of the progestin receptor than all metabolites of NES, and the metabolites essentially are inactive. No mineral corticoid activation was identified that could affect kidney function, i.e., there was no effect on sodium retention, urine potassium levels, or serum creatinine levels. Of note, the preclinical studies that were conducted with NES as a new chemical entity will not need to be replicated in developing future products that contain NES.

Manufacturing: We conducted rigorous investigations on the release of the hormones from the CVS as well as stability testing. These analyses were important to document the quality CMC of the new contraceptive. In total there were 75 report documents in the major CMC section of the NDA (Module 3) and 7 CMC summary reports in Module 2 of the NDA.
Result 2: Expand Availability and Accessibility to the PVR

The project focused on Kenya, Nigeria, Senegal and India for expanding access to the PVR because preparatory research activities had already occurred in these countries. In Kenya, Nigeria and Senegal, an acceptability study of the PVR among women, providers and communities had been conducted complemented by market research with funding from the Bill and Melinda Gates Foundation. In India, a clinical trial comparing the PVR against the IUD had been initiated with funding from the National Institutes of Health (NIH) and the Indian Department of Biotechnology. DCVR built upon the foundation of research and insights by implementing a new set of activities to enhance availability and accessibility of the PVR in sub-Saharan Africa and south Asia. The project vision was to build on the experiential knowledge of PVR introduction to inform the subsequent introduction of Annovera™ in USAID’s priority countries.

1. Engagement with global stakeholders

The project made a concerted effort to collaborate with global stakeholders and networks to support the introduction of the two vaginal contraceptives. In particular, the project recognized the critical importance of engaging with the WHO as the normative body providing global guidance for programming to countries. Countries look to the WHO for providing technical guidance and further validated the project’s strategic approach of engaging with WHO. Project staff engaged with the WHO from Year 1 throughout the life of the project.

The project’s continuous engagement with the WHO resulted in five noteworthy and significant milestones. Together the five milestones achieved have facilitated procurement of the PVR by national family planning programs, created the conditions for a competitive market place, and provide technical guidance on how the new contraceptive can be provided in regular service delivery. The five milestones are:

1. Inclusion of the PVR into the WHO’s Essential Medicines List in 2015
2. Inclusion of the PVR into the WHO’s Expression of Interest for Manufacturers in 2016
3. Inclusion of the PVR in the WHO’s 5th edition of the Medical Eligibility Criteria in 2015
4. Inclusion of the PVR in the WHO Family Planning Handbook in 2018
5. Development and validation of a Training Resource Package (TRP) for the PVR in 2018

The achievement of these milestones was possible due to the collegial partnership the project had created with multiple stakeholders: the Department of Reproductive Health and Research (RHR) of WHO, the manufacturer Grünenthal, and the MCSP program of JHPIEGO. For example, the application for the inclusion of the PVR into WHO’s Essential Medicines List was made jointly with the manufacturer. Similarly, the support from RHR/WHO was key for the timing of the application to the MEC. The DCVR project collaborated with the JHPIEGO-led Maternal Health and Child Survival Project (MCSP) to develop a Training Resource Package (TRP) for the PVR; and review by WHO and USAID provided validation for this training tool.

A second reason for the achievement of the five milestones was because the project built on the success of each prior milestone to attain the next. For example, the inclusion of the PVR in the Essential Medicine List (EML) led to the application for the inclusion of the PVR into the Medical Eligibility Criteria (MEC) guidelines. Inclusion into 2015 EML and the 2015 MEC guidelines facilitated the application to the WHO and review of the PVR being added to the WHO’s Expression of Interest (EOI) for Prequalification (PQ). Finally, based on the inclusion of the PVR into the EML, MEC and EOI, WHO included the PVR in the 2018 edition of Family Planning: A Global Handbook for Providers (3rd edition).

All these key endorsements from the WHO have strengthened our efforts for introduction of the PVR into countries and to thereby increase access to this innovative contraceptive.
In addition to the WHO, the project engaged in global policy discussions hosted by FP2020, the Global Financing Facility (GFF), UNFPA, and the Reproductive Health Supplies Coalition to seek support for advancing the inclusion of vaginal ring technologies with FP programs in priority countries.

2. Creating the conditions for introduction in Kenya, Nigeria and Senegal

In preparation for product introduction in Kenya, Nigeria and Senegal, we analyzed the policy and program context, generated conceptual models for delivering vaginal rings, created champions and identified activities that could be undertaken to support the introduction of the PVR.

Landscaping of the family planning policy and programmatic environment: We began our in-country activities by identifying facilitators and barriers to PVR introduction. We reviewed policies and service delivery guidelines complemented with interviews with key stakeholders in each country. We found that in all three countries, there was broad policy support for reducing maternal and neonatal mortality including existence of service packages for births that occur at both facilities and communities. Thus there was potential for introducing the PVR to expand contraceptive choice, integrate the PVR into postpartum family planning, breastfeeding support, immunization, maternal and child nutrition services. We also learned that family planning service delivery was being task shifted to front line health care providers including community health workers. This confirmed our hypothesis that there were opportunities to include lower level health cadres in the distribution of vaginal contraception.

Models of service delivery: We developed three models to demonstrate how a new contraceptive such as the PVR could be included in existing delivery channels and service packages; innovative ways of financing the product and service; and offered guidance to policy makers, program managers, and service implementers who wish to introduce the ring into their programs.

Registry of stakeholders: We created a registry of global and national stakeholders who would have a perspective on new product introduction. The registry includes those who can serve as champions, implementing partners, key influencers, and civil society voices. Illustrative stakeholders include commodity distributors such as DKT and Population Services International (PSI); implementing partners such as the MOH; professional associations of obstetricians and gynecologists, midwives/nurses, and pharmacists; and influencers such as journalists.

Engagement with providers: Recognizing that health care providers can serve as facilitators or barriers to the uptake of a new contraceptive, the project made a concerted effort to engage with many provider cadres especially those at the community level. In each country, we oriented different family planning provider cadres through their professional associations such as obstetrician-gynecologists (e.g., Society of Gynaecology and Obstetrics of Nigeria (SOGON) in Nigeria, Kenya Obstetrical and Gynaecological Society), midwives and other health cadres (e.g., ANSFES in Senegal), and patent vendors who are members of the National Association of Patent and Proprietary Medicine Dealers (NAPMED) in Nigeria). Where feasible and relevant, we trained health cadres: for example in Nigeria we included a module on the PVR when patent medical vendors were being trained on the DMPA-SC (brand name Sayana® Press); in Senegal, we trained 300 midwives and trainers who had come from the 14 regions of the country for a national meeting.

National Family Planning guidelines: The project was successful in ensuring that the PVR was included in national family planning guidelines when these were being updated. In 2015, the existing family planning guidelines in Kenya and Senegal were revised to include the PVR. In Nigeria, the 2016 edition of the revised National Reproductive Health and Family Planning Service Protocol included the PVR.

Training Curriculums: In addition, in anticipation of its eventual availability in the country, respective Ministries of Health were willing to include the PVR in training curriculums for health workers. For example, the Nigerian National Family Planning Training Manual included the PVR; in Senegal, the PVR was included in postpartum FP (PPFP) training tools for providers (PPFP counseling and PVR administration tools). In Kenya, the MOH and national partners decided to include the PVR in the Kenyan version of the WHO MEC wheel jacket.

Nigeria Costed Implementation Plan (CIP): In Nigeria, the USAID Mission provided support to the DCVR and Expanding Effective Contraceptive Options (EECO) projects for introducing the PVR in that country. We conducted activities in four workstreams listed below; the first three workstreams were led by Population Council, and the fourth was led by WCG Cares:
1. Market landscaping and value proposition activities to create market success
2. Training curriculum and training of trainers for PVR
3. Pilot testing PVR service delivery in Nigeria, and
4. Quality assurance and pharmacovigilance support for PVR.

We commissioned Dalberg Associates to conduct a landscaping of the Nigerian contraceptive market to identify potential market challenges for the PVR and possible solutions to overcome them. The results from the PVR market landscaping indicate that there are 5 key market barriers, (high pricing for the market, lack of clear differentiation with other postpartum contraceptives, risk of skewed user perceptions—from awareness to sustained adherence, registration limitations in terms prescription status, which will constrain access, and risks inherent in an exclusive supply chain) and proposed solutions to overcome these barriers. The introduction strategy will be informed by the identification and knowledge of these market barriers.

The global TRP for the PVR mentioned earlier was adapted for the Nigerian family planning program. The Nigerian curriculum was validated by national stakeholders through a consultative process chaired by the Federal Ministry of Health.

In preparation for service delivery when the PVR is introduced, a training of trainers was completed with one trainer from each geo-political zone and one from the Federal Capital Territory were selected from a database of trainers maintained by the Federal Ministry of Health (FMOH). The trained pool of trainers will lead FP provider training in their respective zones after the PVR is registered and available in Nigeria.

In consultation with FMOH and national partners, the project has identified and selected two clinics for pilot service delivery upon registration of the PVR. The manufacturer, Grünenthal has donated 1,000 PVRs for the pilot service delivery which are available in the country.

WCG Cares developed the pharmacovigilance plan for PVR introduction in Nigeria including Standard Operating Procedures (SOPs) for Adverse Events Reporting as well as the Pharmacovigilance System Master File. The SOPs will be implemented by the Society of Family Health/Nigeria in compliance with Nigeria’s National Agency for Food and Drug Administration and Control Guidelines on Good Pharmacovigilance Practice and can be used for the PVR as well as other products. WCG Cares also developed a regulatory guide on the basics of contraceptive product registration using the PVR registration in Nigeria as an illustrative example.

3. Submission of PVR Dossier

We are happy to report that the project has been successful in submitting the PVR dossier in two sub-Saharan African countries (Nigeria and Senegal), and with plans for submission in two other countries (Kenya and India).

**Nigeria:** The PVR dossier was submitted to Nigeria’s National Agency for Food and Drug Administration and control (NAFDAC) in 2018. Official acknowledgement of the submission, thus beginning the formal review process, was received shortly thereafter. Since submission, consortium partner WCG Cares has been corresponding with NAFDAC responding to their questions. At the time of writing, we are awaiting NAFDAC’s decision. Society for Family Health (SFH) Nigeria was chosen to serve as the temporary Market Authorization Holder (MAH). Upon approval of the PVR, SFH may continue as the MAH.

**Senegal:** The Council has invested its own resources to complement those of the project to hasten PVR market entry in this key Ouagadougou Partnership nation. The PVR dossier was submitted to Senegal’s *Le Direction de la Pharmacie et du Médicament (DPM)* in 2019. Les Laboratoires Didy, a private commercial entity, will serve as the MAH.

**Kenya:** Consortium partner, WCG Cares has made progress on the preparation of the PVR dossier as per the requirements of the Kenyan regulator—the Pharmacy and Poisons Board (PPB). At the time of writing, we anticipate submission of the dossier in the first quarter of 2020. Discussions are ongoing with DKT/Kenya to serve as the MAH.

**India:** The project collaborated with the Indian Council of Medical Research (ICMR) on a clinical trial comparing the PVR with the Copper-T IUD. The results of the clinical trial have been written in a Clinical Study Report (CSR) which will be included in the PVR dossier for filing for registration with the Drug Controller General of India (DCGI), the national regulator. At the time of writing, HLL LifeCare Limited (HLL) will submit the PVR dossier to the DCGI in 2020.
4. Setting the stage for WHO-Pre-Qualification (PQ) application

The PVR has been approved in many central and South American countries; but the PVR dossier has never been submitted to a Stringent Regulatory Authority (SRA) for approval. SRA approval or WHO Pre qualification is a requirement for procurement by large Institutional procurers and bilateral donors. Products that are manufactured by southern manufacturers for southern markets can seek WHO-PQ in the absence of SRA approval to improve the potential for institutional procurement.

Project staff consulted with the WHO to devise a strategy and path to seeking prequalification. Two consultative meetings were held between the WHO, the DCVR project team, and the manufacturer Grünenthal in 2015 and 2016. After examining the existing PVR dossier, the WHO advised two key actions as pre-requisites before applying for prequalification: (1) provide data on at least 400 women who had used the PVR for 12 months and (2) conduct a pharmacokinetics (PK) study on the PVR.

In mid-2019, Grünenthal, completed the PK study and results are available in Spanish. The project team has a plan to combine data from different studies to compile a dataset with information on 400 women who have used the PVR for one year.

At the time of writing, the two pre-requisites identified by WHO have been partially addressed. We believe that the progress made during the DCVR project will enable completion of the remaining activities: translation of the PK study results into English, inclusion of PK results into PVR dossier, compilation of data from 400 women with one year of PVR use, and a clinical study report on the 400 women. We envisage that the manufacturer with technical assistance from the Council will be better positioned to apply for WHO prequalification.

Approaches and Tools for Market Entry

The project adapted approaches and tools from the pharmaceutical sector to prepare for the introduction of the PVR and Annovera™.

1. Market Development Plan (MDP)

We developed a Market Development Plan (MDP) based on an extensive literature review of marketing strategies and key stages of implementation used by key industry partners in the introduction and scale-up of Family Planning/Reproductive Health products and services. The MDP described the five core processes of marketing a product (Product Price, Place, Provider and Promotion). The MDP served as an internal program management document to provide conceptual and operational guidelines for the key stages of product introduction, scale-up and management as well as the specific needs of the delivery of the two products: the PVR and Annovera™.

2. Value Proposition

Recognizing the importance of advocacy, product messaging and product placement, especially when project activities will be transitioned to implementing and supporting partners, the Council contracted Global Health Visions to also develop a value proposition toolkit and statements for vaginal rings. The toolkit extended the MDP and lead to the creation of a value map. The value map laid out the priorities of various stakeholders (e.g., users, providers, communities, policy makers), ranked the priorities, and drew out implications for product placement and introduction.

The project developed a value proposition toolkit with messages or value propositions for three key stakeholders—users, decision-makers, and provider on contraceptive vaginal rings. In addition, it provided the latest research findings, ready-to-use messages, and suggested activities for reaching and involving target audiences. The toolkit will help stakeholders understand how to frame the discussion around new family planning methods.

3. Risk assessment

We conducted a risk analysis for product introduction. The project contracted Global Health Visions to adopt the USAID publication Idea to Impact: A Guide to Introduction and Scale to create a risk framework for the introduction of contraceptive vaginal rings. The report enumerated a list of risks, how risks can be mitigated, and provided recommendations. A noteworthy finding of the report was that over the years, the Council had carefully planned the entire continuum from product development to introduction. A distinction was also made as to the locus of control for risk identification and mitigation, and the role of various stakeholders from manufacturers, procurers, policy makers and research and technical assistance agencies in managing risk.
Technical Assistance

Technical assistance (TA) and capacity building were implicit goals of the DCVR project. The project provided technical assistance to Grünenthal, the manufacturer of the PVR, to QPharma, the contract manufacturer of Annovera™, and to the ICMR.

We provided TA to Grünenthal in varied areas required for regulatory approval. Salient examples include Council provision of TA for the design of a Pharmacokinetics (PK) study on the PVR to address a gap in the dossier identified by WHO and development of the clinical study report that will be submitted to regulatory authorities in several Latin American countries and to the WHO; and TA for manufacturing and developing a stability study protocol for increasing the shelf life of the PVR from two years to three years. The overall objective was to seek ways to reduce costs by making improvements in manufacturing processes as well through larger procurement orders. Large procurement orders can enable bulk purchasing of materials and active pharmaceutical ingredients (APIs). The Cost of Goods (COGs) under the current low volume production process are approximately $6.90 per unit. These costs may be significantly reduced by pursuing larger commercial markets in Latin America, subsidized government public sector procurement in sub-Saharan Africa, and large orders through institutional procurers once the produce is WHO prequalified.

DCVR also engaged early on with advocates working on reproductive health and reproductive justice issues in the US to obtain their perspectives and how to introduce new contraceptives. In particular, in the very first year of the project, we collaborated with the Reproductive Health Technologies Project to design a series of three activities – webinar, post-webinar survey, and in-person stakeholders’ convening. The webinar titled “Integrating Reproductive Justice: Ensuring Community-Informed Contraceptive Development” was well received and provided invaluable insight on the potential role of reproductive justice in contraceptive provision and access. A range of community-based groups, NGOs, and advocacy organizations participated, including Ibis Reproductive Health, National Women’s Health Network, Population Action International, Native Youth Sexual Health Network and United for Reproductive & Gender Equity. Insightful learnings that we obtained from the advocates were woven into our regulatory and introduction strategies are the following:

- Creating and providing information about new technologies in a user-centric way that responds to women’s needs.
- Integrating the consumer’s voice in communications activities as well in strategies for engaging with community leaders.
Over the past six years, we partnered with multiple sub-contractors, vendors, scientific writers, and our manufacturing partner QPharma, whose expertise we required to complement the activities that project staff undertook themselves. By bringing in relevant external expertise, we ensured that quality and timeliness of our deliverables. The collaboration with these various sub-contractors and vendors provided the project with the opportunity to orient new stakeholders on Annovera™ and create champions who can support the product when it becomes available.

For the PVR, project staff collaborated with various partners at the global and country levels. At the global level, project staff collaborated with the WHO and other USAID-funded projects such as the JHPIEGO-led Maternal and Child Survival project and other implementing partners. At the country level, we actively partnered with the relevant Ministries of Health, implementing partners (e.g., ChildFund in Senegal), health advocates, and professional associations (e.g., SOGON in Nigeria).

**Knowledge Outputs**

Documentation and preparation of products for different audiences was a priority for the project. Technical reports, peer-reviewed publications, policy briefs, and informational materials were developed and disseminated over the project period. Relevant knowledge outputs are hosted on the Population Council’s website. We include, at the end of this report, a select list of published peer-reviewed articles, reports, briefs and toolkits that were produced by project staff; we have not included the many presentations that were done over the life of the project at global and national fora.
The project leveraged the resources generously provided by USAID to advance access and availability to innovative contraceptives in LMICs. We leveraged resources provided by foundational donors such as the Bill and Melinda Gates Foundation, the Packard Foundation, the Hewlett Foundation and the Avis and Clifford Barrus Foundation, as well as by the WHO, and from the Council’s own resources.

The Bill and Melinda Gates Foundation (BMGF) provided support for activities to complete the clinical work for the FDA submission. Further, with BMGF support, the project explored and developed new approaches to redesign the SA/EE CVS and for alternate manufacturing processes to reduce markedly the current cost of production. BMGF also supported market research on Annovera™. With funding from the Packard Foundation, the project partnered with FP2020 to highlight the importance of family planning in the development agenda; and for developing materials advocating for sustainable financing. The project also drew upon modest resources from the Council to advance registration of the PVR in Senegal.
Transition Plan After Project Period

Although the project has been successful over the past six years in achieving the results described above, much remains to be done for successful integration of the PVR and Annovera™ into the health systems of USAID’s priority countries. In the following, we describe our plan to for the implementation of a set of interconnected activities in the next 18 months. We believe that the relevance of our two vaginal contraceptives is high with the growing programmatic focus on self-care technologies.

Ring Collaborative

The idea of a ring collaborative continues to be of interest and value to the Council and other product developers. Since early 2019, we have been in discussions with International Partnership for Microbicides (IPM) and AVAC for holding a consultation since there has been progress on registering three vaginal rings: the Council’s Segesterone Acetate/Ethinyl Estradiol Contraceptive Vaginal System (Annovera™) received approval from the US FDA in 2018, the PVR dossier has been submitted to the National Agency for Food and Drug Administration and Control (NAFDAC) in Nigeria and to the DPM in Senegal and opinions from the two regulators are awaited, and IPM has sought opinion from the European Medicines agency on the dapivirine ring (HIV prevention ring).

Post-marketing Studies on SA/EE CVS

The Council will be initiating two studies in 2020. The FDA had requested that we conduct two clinical post marketing studies. The Council (with non-DCVR funds) and TherapeuticsMD developed and submitted to the US FDA two protocols entitled 1) A Drug-Drug Interaction Study to Evaluate the Effects of Strong CYP3A Induction and Inhibition on the Pharmacokinetics of Segesterone Acetate and Ethinyl Estradiol from the Annovera™ Contraceptive Vaginal System, and 2) A Study to Evaluate the Effects of Annovera™ and Tampon Co-Usage on the Pharmacokinetics of Segesterone Acetate and Ethinyl Estradiol were submitted to the FDA on August 30, 2019. The agency has confirmed that the protocols are acceptable. The Council organized a bidding process to identify sites to conduct these trials, performed site qualification visits to confirm suitability for the two selected sites and is planning to initiate the two studies by Q1 2020.

Two other studies are also planned: an ex vivo study to characterize the in vivo release rate of Annovera™; and a study to assess the risk for fatal and non-fatal venous thromboembolism and arterial thromboembolism associated with short-term and long-term use of Annovera™ in a study population representative of actual users of the product in the US and other countries where Annovera™ is prescribed.

Technology Transfer of the PVR

We will continue the discussions that have begun between the Population Council, ICMR and HLL Lifecare Ltd as to the steps required to seek marketing approval for the PVR in India and to reexamine the conditions under which technology transfer from Grünenthal to HLL Lifecare Ltd can take place. We envisage that in 2020, we will be able to assess the feasibility of the technology transfer to HLL Lifecare Limited, the time-frame, and the resources that will be required for a successful transfer.

Planning for Introduction in Kenya, Nigeria, Senegal and India

The culmination of six years of research, programmatic and advocacy activities has resulted in a solid foundation with which to launch the introduction of the PVR and Annovera™ in the four focus countries. We believe that introduction in these countries of the PVR will provide a proof of concept about the feasibility of integrating a new contraceptive format in LMIC program contexts—Senegal as the gateway country to the Ouagadougou Partnership countries, India to the South Asian region, Nigeria as a large contraceptive market, and Kenya as the gateway country for East Africa. Second, the experience that we have accumulated thus far about the preparation for the introduction of the PVR will be valuable to inform the introduction of Annovera™.

Kenya: In 2020, we will submit the PVR dossier to the PPB, the Kenyan regulator. On receipt of approval of the PVR, we will focus on ensuring that the product is included in the national essential medicines list thus facilitating procurement by the Ministry of Health. Simultaneously, we will engage with the MOH and relevant private provider networks to prepare them for service delivery. Further details are available in Annex A.
Project staff will continue to provide updates to relevant stakeholders on Annovera™ as the next innovative contraceptive that can address contraceptive need in Kenya. We will continue to seek resources from bilateral donors such as DFID who have expressed interest in the Population Council’s strategy for introducing vaginal contraceptives in the country. By seeking resources from other donors, we aim to amplify the impact of the investments already made by USAID through the DCVR project.

**Nigeria:** At the time of writing we are awaiting the decision from NAFDAC, the Nigerian regulator on the PVR dossier. In 2020, with the assistance of WCG Cares and Grünenthal, the Population Council will facilitate a GMP facility audit of the manufacturing site by NAFDAC. The Population Council with its own resources has already paid the fees associated with the facility audit. Upon approval of the PVR, we will seek to include it on the national EML.

After support from the USAID Mission for CIP activities period ended in December 2018, the project sought additional stakeholders who could engage in the introduction of the PVR in Nigeria. We have been successful in identifying Rotary International who will assist in pilot service delivery activities beyond the life of the DCVR project. A Memorandum of Understanding has been signed between the Population Council and Rotary International to this effect. We also have 1,000 PVRs that have been donated by Grünenthal that will be used in service delivery. We anticipate a pilot service delivery phase upon the approval of the PVR.

**Senegal:** At the time of writing we are awaiting the decision from DPM, the Senegalese regulator on the PVR dossier. As in Kenya and Nigeria, upon approval of the PVR, we will seek to include it on the national EML. We will continue dialogue with ChildFund for pilot introduction of the PVR through their service delivery platform that utilizes community health workers to improve access.

**India:** We will be providing technical assistance to HLL Life-Care Ltd in the submission of the PVR dossier to the Drug Controller General of India, the regulator. We have an MOU with ICMR for the conduct of programatically relevant research in reproductive health. Under the auspices of the MOU, we will collaboratively with ICMR seek opportunities for introducing the PVR and Annovera™ in select districts of India. ICMR has expressed interest in an introductory pilot study.

**Global:** We will seek partners such as JHPIEGO to develop a Training Resource Package for Annovera™ similar to the one developed for the PVR. Relatedly, we will examine the product support materials that will be created by TherapeuticsMD, and if relevant, adapt them for low- and middle-income settings.

We will continue our engagement with networks such as FP2020, the Reproductive Health Supplies Coalition, and the GFF; as well as bilateral and multi-lateral development partners to ensure that the PVR and Annovera™ are the next new contraceptives that will be considered for introduction, procurement, and advocacy.
Conclusion

The Population Council is pleased to report at the end of six years that investments made by USAID have resulted in the historical approval of Annovera™ by the US FDA and significantly advanced progress towards registration of the PVR in USAID’s priority countries. The project has created the conditions for launching a new vaginal contraceptive format that will contribute to expanding contraceptive choice and address unmet need. By working in partnership with global and national collaborators, we have created engaged champions who can advance the introduction of these innovative contraceptives in LMIC markets.

The Population Council deeply appreciates the support from USAID for advancing scientific knowledge about new vaginal contraceptive formats, seeking regulatory approval, and for setting the stage for introducing new products to expand contraceptive choice for women and families. We aim to amplify the investments made by USAID by seeking additional funding from other donors and funding sources to contribute to better health and wellbeing of women, men and children.
DCVR Project Knowledge Outputs

Journal articles


14. David F Archer; Ruth B Merkatz; Luis Bahamondes; Carolyn L Westhoff; Philip Darney; Dan Apter; Jeffrey T Jensen; Vivian Brache; Anita L Nelson; Erika Banks; György Bártfai; David J Portman; Marlena Plagianos; Clint Dart; Narender Kumar; George W Creasy; Diana L Blithe. 2019. “Efficacy of the 1-Year (13-Cycle) segesterone acetate/ethinyl estradiol contraceptive vaginal system: Results from phase 3 trials,” *The Lancet Global Health*, Vol. 7(8): e1054-e1064.

15. Carolina Sales Vieira, Ian Fraser, Marlena Plagianos, Anne E. Burke, Carolyn L. Westhoff, Jeffrey Jensen, Vivian Brache, Luis Bahamondes, Ruth Merkatz, Regine Sitruk-Ware, Diana L. Blithe. 2019. “Bleeding profile...
associated with 1-year use of the segesterone acetate/ethinyl estradiol contraceptive vaginal system: pooled analysis from phase 3 trials,” Contraception (available online; currently in press).

**Reports**


12. Market Development plan

13. Clinical Study report from the QT/QTc study of the SA/EE CVS.

14. Clinical Study Report from the clinical trial comparing the PVR against the IUD in India.

15. Assessing the residual content of progesterone containing vaginal rings after use.

**Briefs**

1. Introducing the Progesterone Contraceptive Vaginal Ring in sub-Saharan Africa.

2. Delivering Contraceptive Vaginal Rings to breastfeeding women.

3. Progesterone Vaginal Ring: Beneficial role in supporting breastfeeding.

4. Progesterone Vaginal Ring: Beneficial role in birth spacing.


**Toolkits**

1. Training Resource Package for the PVR

2. Value Proposition Toolkit for vaginal rings

3. Product Registration: Basics for Global Health Program Managers. (EECO and DCVR projects)

4. Stakeholder register

5. Medical detailing materials