

**Phase I – Planning Grant for Collaborative and Multidisciplinary Pilot Research (CaMPR).  
Irving Institute for Clinical and Translational Research of Columbia University.**

**Title: Identifying the physiological and pharmacological basis of  
venous thrombo-embolism in women who use estrogen-containing  
medications - focus on combination hormonal contraceptives**

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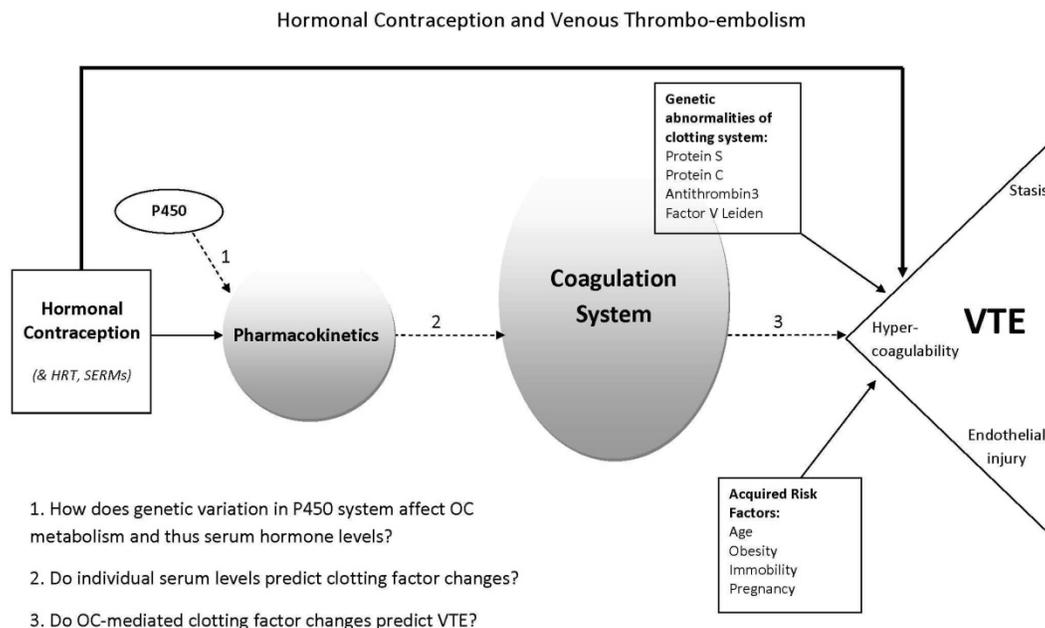
## Specific Aims

The overarching aim of the project is to elucidate the pharmacological and physiological basis of venous thrombo-embolism (VTE) among women using oral contraceptives (OCs), and other estrogen-containing contraceptives and related drugs, in order to develop a valid approach to assess whether particular OCs are associated with greater risks of VTE. Similarly, the project results will help develop a more nuanced clinical approach to discriminate women at high versus low risk of contraceptive-associated VTE.

“Phase I” (Planning Grant) will critically review and synthesize the extensive relevant literature to identify the important knowledge gaps, as indicated in the figure below. We will define the key coagulation system perturbations and candidate assays, and the measurable metabolic pathways that are key to OC pharmacokinetics. We will carry out relevant analysis of existing datasets available to the investigators. We will develop and assess feasibility of recruiting “cases”, that is, women who have experienced an OC related VTE. “Controls” will be readily available from local sources.

“Phase II” will include laboratory-intensive study of normal women before and during OC use to perfect specific assays identified as most likely relevant to the proposed causal pathway; and assess between-women variability and performance characteristics of these candidate assays in order to prepare and justify a definitive case/control study.

“Phase III” will be to obtain external funding for a large case/control study comparing affected and unaffected women with regard to contraceptive pharmacokinetics/genomics, and perturbations of the coagulation system, as well as comparisons of the known genetic and acquired VTE risk factors in order to evaluate possible interactions between these factors and risk from OCs.



## **Background and Public Health Significance.**

Case series of young women experiencing venous thrombo-embolism (VTE), as well as myocardial infarction and stroke, began to identify oral contraceptive (OC) use as a risk immediately following OC introduction in the 1960's. Many epidemiological studies over four decades were designed to characterize and quantify the risks of these adverse events (Royal College of General Practitioners 1974, Vessey 1976 & 1989, World Health Organization 1996). The first results implicated high ethinyl estradiol dose as the main cause for VTE in OC users - the estrogen in OCs is almost exclusively ethinyl estradiol. This led to substantial decreases in the estrogen doses in OCs (Gerstman 1991, Piper 1987, Zacur 1992). Results from the 1990's led to new concerns about the role of the progestin component of the OC in VTE risk – an issue that is not yet resolved (Farmer 1997, Heinemann 2010, Jick 1995 & 2006, Reid 2010). Risk may vary by a factor of 2 depending on which progestin is included in the OC. The timing of VTE risk is now clearly seen to be greatest during the first months of OC use; the overall relative risk (RR) of VTE in OC users is 2-4, with an RR possibly as high as 12 during the first months of use (Bloemenkamp 2000, Gomes 2004, Heinemann 2007). The introduction of a contraceptive patch was heralded as a possibly safer contraceptive, due to thoughts that avoidance of the hepatic first pass metabolism would mitigate the effects of the exogenous hormones on the coagulation system. Unfortunately, VTE risk in contraceptive patch users proved to be at least as high as the risk in OC users (Jick 2006 & 2010). We do not yet have epidemiological data regarding the safety of the ultra-low estrogen dose contraceptive ring, but clinical experience indicates that VTE may also be increased in users of that contraceptive. The newest OC formulations contain estradiol, rather than ethinyl estradiol, and there is interest in whether these preparations will be safer; however, usage is new and data are lacking. Consistent with the estrogen dose-response seen in OC users, clinicians expected that the much lower estrogen dose used in hormone replacement therapy (HRT) would not increase the VTE risk. Numerous well done studies, however, now clearly show that most HRT preparations are associated with a VTE RR of 2-3 (reviewed in Westhoff, 2007). VTE risk is highest early in the use of HRT, and there is emerging epidemiological evidence that an estradiol patch HRT may be safer than other formulations (Canonico 2010, Olie 2010, Scarabin 2003). VTE risk is also elevated during the use of selective estrogen receptor modulators (SERMs) for breast cancer prevention (Fisher 1989, 1996 & 1999, Vogel 1993). Pregnancy is associated with a greater VTE risk than any of the hormonal medications with an RR of ~7 (Dinger 2007, Heit 2005). Non-hormonal risk factors for VTE include increasing age, obesity, surgery, immobilization, family history of VTE, and specific genetic abnormalities in clotting factors including protein C, protein S, and antithrombin III deficiencies, the factor V Leiden mutation, and the prothrombin G20120A mutation. Recognition of these risk factors has led to evolving guidance regarding which women can safely use an OC (CDC 2010, van Vlijmen 2011, WHO 2004). Despite dose reductions and exclusion of certain high risk women from using an OC (e.g., obese women and those with a family history of VTE), VTE remains a significant risk. At least 10 million U.S. women and 100 million women worldwide use the OC. Recent estimates of VTE incidence among OC users are about 10/10,000 woman-years (Heineman 2007, Dinger 2007). In the U.S. we thus expect about 10,000 VTE cases annually in OC users (10 million women with an annual risk of 10/10,000) with substantial morbidity and mortality. An enormous secondary risk is the avoidance of these effective contraceptives due to fear of VTE. A documented

consequence of each media “pill scare” is a dramatic surge in unintended pregnancy and abortion (Mills 1997, Reid 2010, Skjeldestad 1997). Thus better understanding of the OC/VTE relationship will not only prevent VTE itself, but can also help to prevent unintended pregnancy, an epidemic problem in the U.S. Breast cancer prevention is an analogous issue, where physicians and women avoid using SERMs for prevention due to concern about the VTE risk (Kinsinger 2002).

### **Overview of Multidisciplinary Approach**

This project brings together new colleagues from the Departments of Medicine, Pathology, Pharmacology and Obstetrics and Gynecology in the College of Physicians and Surgeons, and from the Departments of Epidemiology and Population & Family Health in the Mailman School of Public Health. In addition the team will include an epidemiologist from Memorial Sloan-Kettering Cancer Center, and a hematologist who focuses on thrombosis from the Albert Einstein College of Medicine; these latter individuals have critical expertise that is not further available within Columbia University. Each of the eight individuals will contribute their expertise in three or more of the salient areas listed below:

Clinical Hematology: Billet, Diuguid, Eisenberger

Clotting: Billet

Laboratory science: Bertino, Billet, Cremers, Rai

Pharmacology (including PK, metabolism, genomics, proteomics): Bertino, Cremers, Rai

Contraception: Pike, Westhoff

Epidemiology: Pike, Westhoff

Design and execution of clinical studies: Bertino, Billet, Cremers, Rai, Westhoff

Recruiting cases (i.e., women with OC-associated VTE): Billet, Diuguid, Eisenberger, Westhoff

Statistical analysis and inference: Bertino, Cremers, Pike

The major task for the collaborative group members during Phase I will be to review and synthesize the relevant literature, as directed by the priority question areas in a sequence listed below, and according to their areas of expertise. The goal is to further develop a compelling, testable, and fundable approach to the questions of how OC use leads to VTE. In particular, this must include the issues of individual risk and formulation risk.

**First Priority question:** Which clotting factors (CFs) are most strongly linked to VTE? The co-investigators will identify and prioritize candidate CFs, combinations of CFs, or other coagulation system perturbations (“CF” as used throughout this document refers to all of these). Only those CFs that are suggested by case/control studies as associated with the risk of VTE, or those that are suggested by studies of VTE recurrence, or those that are suggested by knowledge of the biology of clotting as related to VTE are pertinent here. The group will also assess possible surrogate markers for the candidate CFs. Subsidiary questions include what is our state of knowledge regarding within and between person variability of these factors? What cofactors influence the values and the variability (e.g., age, race, weight, menstrual cycle day, smoking)? In a recent review Kluft (2011) asserts that between-person variability is substantial, and that within-person variability is modest. The planning group will assess details about such variability in order to plan new studies. What are the measurement issues for the candidate CFs? How

many approaches to measuring a candidate factor are in use, and do they give consistent results? Which assays are in use at CUMC/NYPH? Which assays are available elsewhere? At what cost (internal and external)? The study hematologists and laboratory experts will need to census which tests are available at CUMC versus elsewhere. The thrombin generation assay (see below), for example, is not available at CUMC; however, frozen plasma is adequate for that test, and there are other centers that have this equipment, such as Beth Israel in Newark, N.J. where Dr. Eisenberger worked previously. Of particular interest are those assays that aim to quantify a more integrated view of coagulation system activation or of pro-coagulant activity, rather than the more reductionist quantification of individual clotting factors. The thrombin generation assay (TGA), which is one approach to assessing coagulation system activation and “activated protein C resistance” (APC), is an example. This assay merits special attention here: in a cohort study of 188 patients with idiopathic VTE, having a TGA result above the median was strongly associated with the risk of a recurrent VTE in the next 3 years (27% versus 11%) (Besser 2008). A similar cohort of 914 patients found 6.5% recurrence in those with lower TGA results and 20% recurrence when the TGA was higher (Hron 2006). Thus, this assay has potential to be a clinically meaningful marker of VTE risk although its predictive power has not been evaluated prior to a first VTE. Of note, there are several approaches to the TGA, including more than one commercially available analyzer, and some evidence that results are not consistent across assays; thus, study of the fine details of TGA and other assays is necessary and will depend on consideration by those with expertise in laboratory medicine.

**Second Priority question:** Which CF changes occur with OC use? Due to the known risk of VTE, the regulatory agencies (FDA, EMEA) require a large and increasing number of clotting factor measurements regarding any new hormonal contraceptive agent. Pre-approval studies are never large enough to quantify the risk of VTE in new products; thus, these coagulation factor tests serve only as surrogate risk markers, and we have an enormous literature, sampled in the **Table** below, that describes several of the clotting factor changes that occur with use of hormonal contraception. In the most extensive such study, the OC Hemostasis Study Group (2002) compared CF changes among 7 different OCs and clearly showed that both EE dose and progestin type relate to magnitude of CF changes. The studies in the Table compare baseline and mainly 6 month levels of each factor. Given that the greatest risk of VTE during OC use is during the first few months, the lack of data regarding short term changes in the CF is a critical knowledge gap. Many other studies of the OC/CF associations are published, but are cross-sectional, are thus more difficult to interpret, and are not cited here. Since we already know that EE dose matters on a population level, we would expect to find that it will matter on an individual level. The PK of OC hormones is well established to be highly variable between individuals (Abrams 2002, Hammerstein 1993, Jung-Hoffman 1989, Kuhn 1992 & 1993, Orme 1991, Siekmann 1998, Westhoff, 2010). With many other drugs toxicity is related to individual serum levels, thus we monitor those levels and adjust doses (e.g., amikacin, carbamazepine, digoxin, tacrolimus). In contrast, there is no information about individual OC PK and adverse events, or regarding individual OC PK and CF changes, another critical knowledge gap.

**Third Priority question:** Which OC mediated CF changes coincide with the clinically predictive CF measures? Are there additional relevant markers? The evidence synthesis for the first two questions may largely clarify this issue. In addition, a number of ideas and papers require

critical review by interdisciplinary experts, for instance, the discussion by Odland and colleagues (2002) of whether changes in sex hormone binding globulin (SHBG), touted as a surrogate marker, are predictive of OC-associated VTE. Bloemenkamp and colleagues (1998) evaluated CF in post-VTE women and controls, many in both groups using OC, and suggested that women who experienced OC-associated VTE were “hyper-responders”; that paper shows clear differences between the groups, but no quantitative support for a hyper-response. In contrast, Kluff (2011) suggests that CF levels are variable in a population, but individually stable and intrinsic, such that any changes would be across the board without a differential response.

**Fourth Priority question:** How can we study OC-mediated CF changes in women who have experienced a VTE (i.e., the cases in the future case/control study)? The outcome is rare enough (about 10/10,000 OC users per year) that we cannot practically study this association prospectively; in addition, the disturbances of the clotting system at the time of a VTE and during treatment will prevent evaluation of incident cases. Among women who have experienced and recovered from an OC-associated VTE, the possibility of challenging them with an exposure to an exogenous hormone will require extensive planning and ethical evaluation. It is possible that even a single dose exposure to OC will be sufficient for evaluating the response, which is a key practical issue and thus a question for study in Phase II.

**Fifth Priority question:** How to find women who have experienced an OC-associated VTE? The hematology and contraceptive clinicians must find the means to identify a large number of past OC/VTE women, and will then assess feasibility of accruing these cases. Based on population, 10% of the expected 10,000 OC-associated VTE cases per year in the US will occur in the NY metropolitan region. This would be an ample population from which to recruit women for the planned studies. Most studies of VTE have been done in European populations; carrying out such a study in the NYC region would give an opportunity to study this problem in members of racial and ethnic minority groups. Approaches to recruitment via colleagues in the hematology and contraception clinical communities, as well as direct advertisement, must be developed and tested. We need to evaluate recruitment near the time of an event as well as after VTE treatment is complete. This subgroup will also begin to prepare IRB applications for Phase II and Phase III studies.

**Additional Phase I questions and issues.** A) Phase II will be a study of OC PK, metabolism, and timing of CF changes among normal women, thus we need to choose the most useful one or perhaps two OC formulations for that study, to be based on discussions with additional steroid experts, and also based on assay costs and sample size considerations. B) The question of how quickly estrogen-containing products cause changes in the coagulation system (and how quickly such changes reverse after withdrawal of the drug) is critical for practical and ethical planning of the next studies. Provocative studies regarding the problem of bleeding in males and females with renal failure show that estrogen can be a successful pro-coagulant in this setting with onset of action as soon as 6 hours after IV and 3 days after oral administration (Livio 1986, Bronner 1986, Heistering 1990). Whether this action is mediated through CF, platelet function, or endothelial function seems to be unknown, but is key for consideration during the planning phase. C) We will need to evaluate all of the above questions for SERMs and HRT, as VTE related to these exposures is also of enormous public health significance.

We must consider whether the present knowledge base and resources indicate that we can evaluate SERM and HRT in the same manner as the OC.

**Phase I timeline:** The investigators as a large group, and in interdisciplinary subgroups, will address the key questions posed above with regular in-person meetings as well as virtual meetings. Each question, as refined through initial discussion, will have 2-3 lead investigators, who will move through literature review and synthesis using a process borrowed from the ARHQ-contracted evidence-based practice centers that provide reports to the U.S. Preventive Services Task Force. For each question the investigators will first develop more detailed causal diagrams (following on the more general diagram provided on page 1 of this proposal) as a starting point to guide the reviews and to ensure identification of all variables that must be measured and controlled in future studies (Greenland 1999). The study research assistant, who will be a Mailman School of Public Health graduate student, will have organizational responsibility for the process. Depending on the complexity of the questions, the magnitude of the relevant literature, and the resources available, this review and synthesis process generally takes one to three months to fully address the questions in each causal diagram. Much of the relevant literature is already identified and collated (although not yet following the formal evidence review process), and substantial “parallel processing” of the questions will be possible. The group will, however, generally approach the first four questions in sequence, as each informs the direction of the next. The clinicians and epidemiologists in the group can begin to address the fifth question, regarding patient recruitment, immediately as this does not depend on the analysis of the first four questions. The additional Phase I questions A and B refer to a smaller literature and can be resolved quickly. Additional questions regarding SERMs and HRT will be handled alongside each of the priority questions. This work can begin immediately (in advance of funding). Addressing the first four questions will require 3-5 months at which point it will be possible to write a proposal for a Phase II study. Addressing question 5 may require several months (which can overlap with the other tasks), and this is necessary to write a proposal for a Phase III study.

**Long term Plans, Phase II.** Based on results of the planning activities and the key knowledge gaps identified, the investigators will propose a physiological study of normal women. The investigators will seek funding for this through the Irving Institute CTSA Phase II pilot award program and through NICHD or NHLBI RO3 or R21 programs insofar as this project meets their criteria. The aim of the study will be to assess the magnitude, variability, and timing of individual-level CF changes during OC initiation, and to determine how those changes relate to individual-level OC PK. The study will recruit women without OC contraindications to have baseline CF assessment, and then to begin OC use, followed by serial CF (and all other markers of interest) measurements over the first several days and up to 3 months. The participants will also undergo day 1 and steady state 24 hour OC PK. Data from such a study would be the first to evaluate whether individual-level OC serum concentrations are associated with adverse pharmacodynamic outcomes (i.e. adverse CF changes), and thus would be of direct interest. Secondly, these data would be necessary to propose a larger study that would include women who have experienced an OC-associated VTE. The details of which CF to measure (and when) will result from the planning phase. The collaborative group has all necessary expertise to design and execute such a study at CUMC.

**Long-term Plans, Phase III. RO-1 application** supported by the evidence synthesis and decisions from phase I and the results from phase II as a proposal to NIH, aiming for joint NICHD and NHLBI review/funding. The primary proposal will be for a case-control (C/C) study of women with recent OC-associated VTE (cases) and age- and race- matched women eligible for OC use without VTE history (controls). The specific aims for this proposal will derive from the initial questions posed throughout this proposal, as refined by the interdisciplinary planning process. Similarly, the specific CF and PK measurements to be included in the C/C comparisons will derive from results of phase I and phase II activities. Phase II results will be critical in order to define the appropriate sample size. The proposed study will include a bio-repository of DNA and plasma, so that it will be possible to carry out appropriate analyses in the future as new risks (& associated tests) are identified. The proposal will benefit from incorporating the best operational features of past C/C and cohort studies, such as detailed case definition and verification, and will include superior study design and superior laboratory measurement thanks to the expertise of the members of the collaborative group. Most past epidemiological studies were limited to using questionnaires, which cannot address the questions we pose, and most did not assess critical, now-recognized confounding factors. Most previous studies that included laboratory measurements (such as genetic abnormalities of the coagulation system) had inconsistent selection of cases and controls, as well as inadequate statistical power and incomplete analyses (Reid, 2010). The proposal will benefit from a formal definition of study questions via causal pathways, the assessment of relevant literature, and the extraordinary multidisciplinary expertise of the planning group.

### Budget

Research assistant (50% time for 35 weeks) (enrolled MSPH graduate student @ \$20/hour x 20 hours/week = \$14,000, no FB charged for FT students during term) to organize and staff the regular meetings of investigators and to produce minutes of these; to collate reference materials needed to produce and update the literature synthesis, to develop IRB applications, to assist in grant preparation.

Office expenses. \$1000.

Table. CF changes during OC use	Johnson 2008 N=24	Kluft 2008 N=96	OC Hemostasis Study Group 2002 N=707	Middeldorp 2000 N=23	Weinges 1995 N=20	Basdevant 1993 N=49	Melis 1991 N=89	Ball 1990 N=43	Sitori 1990 N=10	Prasad 1989 N=51	Cohen 1988 N=26
Fibrinogen	↑	↑	↑	↑	↑	=	↑	↑	=	=	↑
Factor VIIc			↑↓*								
Factor VIIa			↑	↑	↑			↑		↑	↑
Factor VII (ag)			↑								
Factor VIII	=		↑	↑	=					=	
FvW-RCoF			↑								
Factor V				↓						↓	
Factor X				↑	↑					↑	↑
Factor II				↑						↑	
Antithrombin (ag)			↓			↓			=		
Antithrombin	↓		↓		↓	↓		↓			↓
Protein C (ag)			↑								
Protein C			↑		=			↑	=		
Protein S (free)	↓		↓			↓					
Protein S (total)	↓	↓	↓			↓					
FgDP			↑								
TAT			=	=							
Soluble Fibrin			↑	=							
APC (ETP)			↑								
APC (APTT)		↓	↓				=			↓	

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