ESC Grant application form - Project v2019 - A

Submission Date	2019-06-30 14:40:14
Name of applicant	Karin Brandell
Job title	PhD-student, MD Resident Obstetrics and Gynecology
Address	WHO center Karolinska sjukhuset Solna, QB:84 Solna 171 77 Sweden
Phone Number	(+4673) 0735568
E-mail	karin.brandell@ki.se

A short CV of the applicant (or the principal investigator) should be provided here. (Max 250 words)	Higher education • 2012 MD, Karolinska Institutet (KI), Stockholm; Sweden • 2018-12-20 Registered PhD student at Div. of Obstetrics & Gynecology, Dept. of Women´s & Children´s Health, KI. Name of doctoral project: “Optimising treatment and increasing access to medical abortion care”. Supervisor: Prof Kristina Gemzell Danielsson Co-supervisor: Dr Anette Aronsson Employment history • Resident, Obstetrics and Gynecology, Dept of Women and Children Södertälje Hospital 2017-10-02 – ongoing • Resident, Obstetric and Gynecology, Dept of Women's health, Skånes University Hospital 2015-11-15 – 2017-10-01 • Intern, South Hospital, Stockholm, Sweden 2013-03-04 – 2015-11-01 • Underläkare / Junior doctor, Internal medicine and cardiology emergency dept. Danderyds Sjukhus 2012-01-23 – 2012-12 • Junior doctor, Internal medicine dept., Sunderby Hospital Publications and reports • Vikhareva O, Skott Rickle G, Lavesson, T, Nedopekina E, Brandell K, Salvesen KÅ. Hysterotomy level at cesarean section and occurrence of large scar defects: a randomized single-blind trial. Ultrasound Obstet Gynecol. 2018 Nov 28. Doi: 10.1002/uog.20184 [Epub ahead of print] • Knowledge and attitudes on female genital mutilation among health care students in Nairobi, Kenya. A quantitative study. Minor field study, SIDA-finansierad. Jan 2011 Teaching merits • 2014 Nominated clinical tutor of the year, Dept of Internal Medicine, Södersjukhuset • 2007-2012 Tutor in anatomy for medical students, Karolinska Institutet Other merits • Minor Field Study Scholarship, SIDA, 2009 • Research grant "Forskar ST" from SLL, Stockholm
Submission date of this form	30-06-2019
Is the person responsible for the project different to the person named in box A	Yes
Name of person	Kristina Gemzell Danielsson
Job title	Professor
Address	Tomtebodavägen 18A Karolinska Institutet Solna 171 77 Sweden

Phone Number	(+46 70) 910 78 21
E-mail	kristina.gemzell@ki.se
Title of the project	Efficacy of Very Early Medical Abortion – a randomized controlled non-inferiority trial

Please provide a comprehensive description of your project. The application will be assessed under the following headings: Background and hypothesis; Specific aims and objectives; a Needs Analysis with evidence of unmet need and Innovation; Approach and Methodology; ie numbers recruited, ethical approval. inclusion & exclusion criteria; Expected outcomes; Impact it will or may have in the field of contraception, sexual and reproductive health; Feasibility (1000 words)

Background:
Since its introduction into clinical routine medical abortion has changed the abortion practices dramatically in Sweden and is also gradually increasing in Europe and globally due to its high efficacy, safety and acceptability. During the last 25 years gestational age at an induced abortion has declined in countries, which have introduced medical abortion. This has resulted in more and more women presenting at a very early gestation for an abortion.
The possibility to do the abortion at a very early gestation has significant advantages for the women not only on a psychological level but also from a medical point of view. Very early medical abortion (VEMA) already before any intrauterine pregnancy can be visualized at an ultrasound examination may be of particular benefit to reduce pain and bleeding. In addition if women are encouraged to present early for their abortion it could give the opportunity to
detect and treat ectopic pregnancy in early gestation. However, a concern that VEMA may be less effective compared to treatment when an intrauterine pregnancy can be detected with ultrasound has led to inconsistent treatment protocols, demand of repeat visits to the abortion clinic, imposed unnecessary or harmful waiting times and impaired access. Most doctors in clinical routine as well as in clinical trials of medical abortion require confirmation of intrauterine pregnancy by ultrasound, excluding women who on transvaginal ultrasound have no visible gestational sac or the presence of an intrauterine anechoic structure without defining features of gestation, such as a yolk sac or fetal heart rate. Consequently there are only three published studies on the use of VEMA in women without confirmed intrauterine pregnancy. Two of these small retrospective studies the largest including 68 women, suggest that women undergoing VEMA might be more likely to experience treatment failure (i.e. ongoing pregnancy) and incomplete abortion. In contrast our research groups own analysis of a cohort of women undergoing VEMA compared with women with a confirmed intrauterine pregnancy undergoing medical abortion and including more than 1500 cases and matched controls indicates that VEMA is effective with no difference in efficacy compared with medical abortion in later gestation.
The risk of ectopic pregnancy is also of particular consideration and therefore, most health care providers delay the treatment until an intrauterine pregnancy can be visualized and confirmed. Clearly, more information is needed on the efficacy and safety of VEMA to develop evidence based clinical guidelines.

Hypothesis: VEMA will be as safe and effective as when a uterine pregnancy can be confirmed on ultrasound examination.

Method: A multi-centre, randomized, controlled trial at 11 study sites in Austria, Finland, Sweden and Scotland. Women > 18 years (n=1500) seeking medical abortion with an estimated gestational length less than 6 weeks with no confirmed intrauterine pregnancy or exclusion criteria (visible (confirmed) IUP, contraindications to medical abortion including diagnosed pathological pregnancy at the initial examination, inability to give informed consent, previous ectopic pregnancy, pregnancy with an IUD in situ) will be included after informed consent has been retrieved.

Study participant will be randomized to either immediate treatment (intervention group) or delayed treatment until intrauterine pregnancy can be confirmed (control group). For the intervention group the treatment will be assessed with s/p-hCG after 1 week. Primary outcome will be complete abortion rate without ongoing pregnancy or surgical intervention for incomplete abortion. Analysis will be a mITT and the non-inferiority margin set at 3%. 1.
Secondary outcomes will include early diagnosis and treatment of of ectopic pregnancy, treatment for incomplete abortion, bleeding, pain, acceptability.

Expected outcomes: The overall aim of this multinational, multicenter, randomized trial is to increase access to early medical abortion by providing data for development of evidence based guidelines for women seeking early medical abortion.

The study has received Regional Ethics Review Board approval at Karolinska Institutet with Dnr.2017/1622-31

Refernces
Safe abortion: technical and policy guidance for health systems.2nd ed.Geneva: WHO;2012

Schaff EA, Fielding SL, Eisinger S, Stadalius L. Mifepristone and misoprostol for early
abortion when no gestational sac is present. Contraception 2001;63:251-254.
Goldstone P, Michelson J, Williamson E. Effectiveness of early medical abortion using low- dose mifepristone and buccal misoprostol in women with no defined intrauterine gestational sac. Contraception 2013;87(6):855-858.
Heller R, Cameron S. Termination of pregnancy at very early gestation without visible yolk sac on ultrasound. J Fam Plann Reprod Health Care 2015;41:90–5.
Bizjak I, Fiala C, ,Berggren L, Hognert H, Sääv I, Bring J Gemzell-Danielsson K Efficacy and Safety of Very Early Medical Termination of Pregnancy: a cohort study. BJOG. 2017
Whitehouse KC, Kim CR, Ganatra B, Duffy JM, Blum J, Brahmi D, et al. Standardizing abortion research outcomes (STAR): a protocol for developing, disseminating and implementing a core outcome set for medical and surgical abortion. Contraception. 2017

Timeline: When will it start / finish? (Max 20 words)	Patient recruitment started Q1-2019 and estimated to be concluded within two years. Data analysis and presenting will take 6 months.
Where will it take place – country / town, establishment? (Max 20 words)	10 study sites in abortion clinics in Austria, Finland, Sweden and Scotland.
Sector in the area of contraception, sexual and reproductive health:	Medical abortion

Is it a 'new' project?	Yes
Do you foresee any reasons (political, climatic, etc) why this project may be adversely affected? (Max 20 words)	No
How much will this project cost?	€625 600
How much are you requesting from ESC?	€10 000
Are there other partners or organisations supporting this same project?	Yes
If YES - name the other partners who will support this project (Max 20 words)	Swedish research council
Have you already obtained any funding?	Yes
Are you still awaiting a response towards this project? (Give details in the table below)	Yes

Budget

List each Item required for this project	Amount requested from ESC	Amount requested from additional partner	Name of partner	Any Comments
Swedish PIs salary PI Salary	0	449000	Swedish Research Council	Co-funding received
International PIs salary	5000	131000	Grand Challenges Canada	Co-funding applied for
Research midwives salary	1000			
Salary Karin Brandell PhD-student	1986	0		
Statistician	1000	5032	Swedish research Council	Co-funding received
Computer programs and equiptment	1000	15400	Grand Challenges Canada	Co-funding applied for
Clinical trial conductor		1800	Swedish Research Council	Co.funding received

	Travel expenses		13400	Grand Challanges Canada	Co-funding applied for

Total amount requested from ESC	€10 000
Total amount requested from partner(s)	€615600
The ESC may not be in a position to fully fund all applications; you must indicate whether / how part funding may impact your project. (Max 100 words)	Part funding from the ESC will allow us to fully cover expenses for all staff and equipment involved in this large multicenter RCT. It is also a great oppurtunity to work together with the nominated mentor in this project.
Who will oversee the budget & keep accounts? Provide name, title, contact number and email address	Sandra Brogårde, Head of administration, Dept of Women's and Children's Health, Karolinska Institutet, sandra.brogarde@ki.se, tel +468-524 884 98
If you or your department has received funding from ESC for a project or course before, please give details of the date of funding, contact person and title of project or course.	Research study; Nexplanon Quick Start 2015 Kristina Gemzell Danielsson

I/We, as responsible agents for this project, agree to the following 10 points:

	yes
I/We agree that all monies will be spent appropriately	✔
I/We agree to work with the nominated Mentor	✔
I/We agree to advise you at the earliest time if this project is delayed or cannot be completed	✔
I/We agree to provide an interim report(s) part way through the project and a final report to the ESC within 6 months of the end of the project.	✔
I/We agree to provide the ESC with an interim budget(s) and a detailed budget at the end of the project. NOTE funding will be awarded in stages and will be dependent on appropriate reporting.	✔
I/We agree to provide receipts for monies spent if requested.	✔
I/We agree that if we need to make any significant changes to the duration, contents or funding of the project after it has been awarded, I/we will advise the nominated mentor.	✔
I/We agree that any unspent money will be returned to the ESC	✔
I/We (the applicant) agree to acknowledge the ESC as a donor in any publications, submission of abstracts and oral communications resulting from this project. Please inform the ESC Office where and when the data is to be presented and/or published and note that ideally any manuscript should be sent to the ESC journal in the first instance.	✔
I/We agree to remain fully paid up ESC member(s) until the final grant report is submitted	✔

Full Name	Karin Brandell
Date	29-06-2019