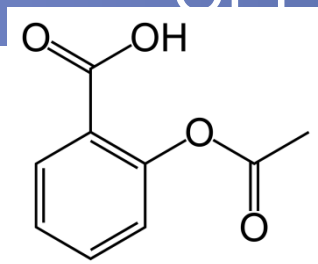
16th June 2016

Proposal for Review

STICs and STONES: Prospective Assessment of Aspirin in Chemoprevention of high risk Ovarian Cancer (CCTG OV.24)

A RANDOMIZED TRANSLATIONAL WINDOW OF OPPORTUNITY TRIAL



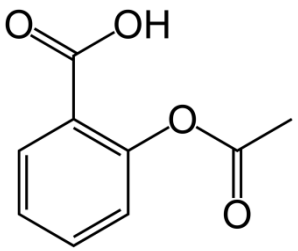
Stephanie Lheureux, Katherine Karakasis, Patricia Shaw, Harriet Richardson, Elisabeth Eisenhauer, Hal Hirte, Daliah Tsoref, Barry Rosen and Amit Oza

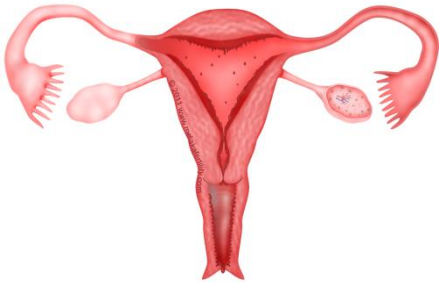
Canadian Cancer Trials Group

Study proposal

A phase II, double blind, placebo- controlled, randomized trial to compare regular use of low-dose aspirin versus placebo in women with germline BRCA1/2 mutations.

In both arms, prophylactic surgery will be performed in the expected timing as part as the standard of care.





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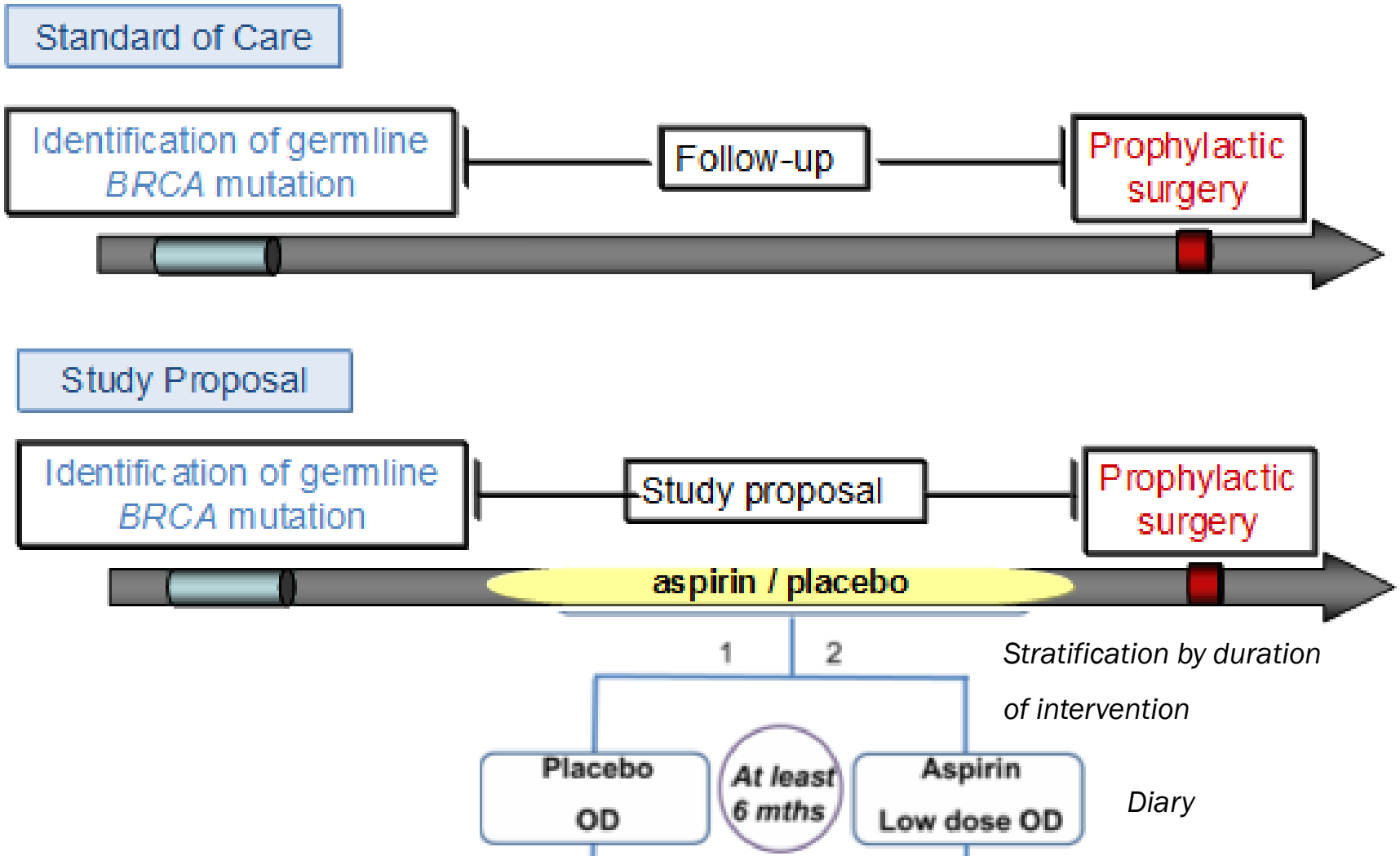
Hypothesis: *Regular use of low-dose aspirin in women with inherited BRCA1/2 mutations will decrease the occurrence of ovarian cancer precursor lesions observed in the fallopian tube at the time of the prophylactic surgery*.



Endpoints

- **Primary**

Presence/absence and numbers of cancer precursor lesions identified by Central Pathology review in the fallopian tube in resected specimens of patients who receive a minimum of 6 months of either low dose aspirin or placebo:

  - Occult (early) carcinoma
  - Serous tubal intraepithelial carcinoma (STIC)

- **Secondary**

  - To identify the non-invasive tubal lesions: the p53 signature
  - To elucidate the linkage between tumorigenesis and microenvironment
    - Hormone stimulation
    - Inflammatory mediators involved in ovulation
    - COX1/2 - VEGF
  - To assess the credibility/ acceptance of the drug intervention and monitor serum ASA levels

Statistical Design

- **Hypothesis**
  - Control: 15% occurrence of pre-& early-malignant lesions
    - 6% occult carcinoma
    - 7-10% STICs

Geoge SH, Front Oncol 2014

  - Aspirin: 40% risk reduction

Trabert D, J Natl Cancer Inst 2014

- **Sample Size**

Placebo Group Pre-lesion rate (%)	Aspirin Group Pre-lesion rate (%)	Absolute difference	Type I error rate	N1:N2 (Total)
15	9	6.0	0.20	248:124 (372)

2:1 allocation; Type I error 1-sided; 40% relative risk reduction

Drop off 10%: 414 patients for inclusion

Feasibility: Estimated Accrual 200/year

Province	Centre	PI	# pt with prophylactic salpingo oophorectomy	Eligible subjects annually
ALTA	Cross Cancer Inst	V Capstick	20	6
BC	BCCA Vancouver	D Miller	25	20
MB	Cancer Care Manitoba: Winnipeg	L Lotocki	10	5
NFLD	D.H. Bliss Murphy Cancer Centtre	P Power	15	10
ON	Ottawa Hospital	M Fung Kee Fung		
ON	Jurvinski Cancer Centre			
ON	PMH	B Rosen	40	40
ON	London Health Sciences Centre	J McGee	20	10
QC	CHUM	Sauthier	12	8
QC	CHUQ	M Plante	20	most
SASK	Saskatoon	C Giede	10	70%

Intergroups: ANZGOG, GINECO, MRC
?? NRG, NSGO

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Current Status of Trial

- Protocol written
- Database specifications finalized
- Drug Supply: Discussions ongoing with regulatory authority and drug manufacturer: stability testing and study supply capsule composition
- Planned trial activation in Canada: first quarter 2017
- Collaborating Groups must self fund for participation