A RANDOMIZED TRIAL COMPARING RADICAL HYSTERECTOMY AND PELVIC NODE DISSECTION VS SIMPLE HYSTERECTOMY AND PELVIC NODE DISSECTION IN PATIENTS WITH LOW RISK EARLY STAGE CERVICAL CANCER

A Gynecologic Cancer Intergroup (GCIG) Trial led by the NCIC CTG

GCIG Trial Designation: The SHAPE Trial
NCIC CTG Protocol Number: CX.5

Chair: Marie Plante

Background

- Treatment modalities for stage IA2/IB1
  - 75% surgery alone
    - 1/3: cone alone
    - 1/3: simple hyst with / without nodes
    - 1/3: rad hyst with / without nodes
  - 25% some form of radiation therapy

FIGO 24th Annual Report

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Background

- Considerable **variation** exists in international practices
- **Lack of high-quality evidence** upon which clinicians can base their decisions and advice women
- Need to **standardize treatments** and a need to identify the patient and disease for which a **less radical surgery** can safely be offered
- In the context of **"survivorship" issues** related to long-term surgical effects:
  - Compromised sexual, bowel and bladder function
  - Infertility

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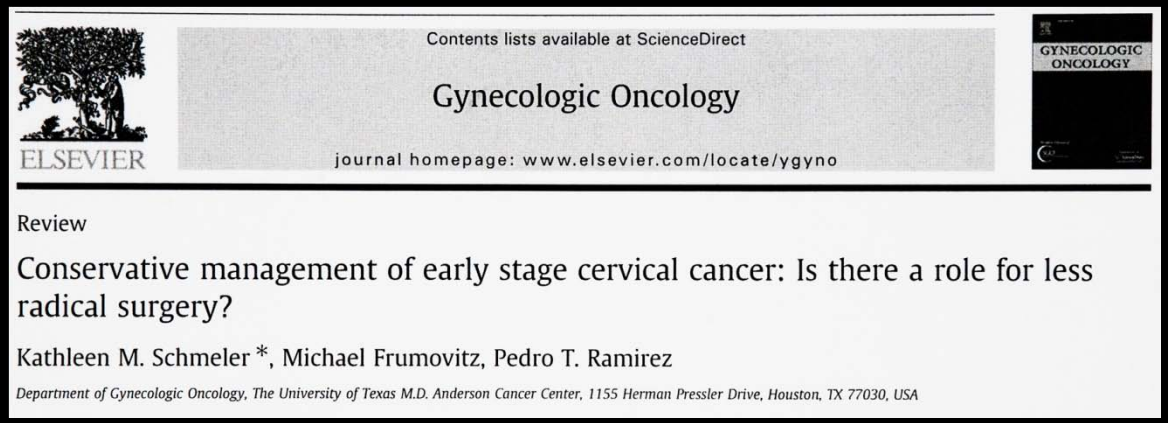
Background



Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Review

Conservative management of early stage cervical cancer: Is there a role for less radical surgery?

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Retrospective studies

Author	Year	Low-risk criteria	N	Parametrial involvement in low-risk group (%)
Kinney [13]	1995	Squamous histology only, tumor <2 cm, no LVSI*	83	0.0%
Covens [14]	2002	All histologies, tumor <2 cm, DOI** <10 mm, negative pelvic lymph nodes	536	0.6%
Stegeman [15]	2007	Squamous, adenocarcinoma, adenosquamous or clear cell histology, tumor <2 cm, DOI** <10 mm, no LVSI*, negative pelvic lymph nodes	103	0.0%
Wright [16]	2008	All histologies, tumor <2 cm, no LVSI*, negative pelvic lymph nodes	270	0.4%
Frumovitz [19]	2009	Squamous, adenocarcinoma or adenosquamous histology, tumor <2 cm, no LVSI*	125	0.0%

*LVSI: lymphvascular space involvement
**DOI: depth of invasion

N=1117 < 1%

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Schmeler K et al. Gynecol Oncol 120:321, 2011

Background

Concept of the trial

- To demonstrate that **simple hyst** and nodes **is not inferior** to **radical hyst** and nodes in terms of pelvic relapse rate and is associated with **better quality of life/sexual health**

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Background

Definition

- « Low-risk » early-stage cervical cancer
  - IA2
  - IB1 < 2 cm
  - Limited stromal invasion
    - < 10 mm SI on LEEP/cone
    - < 50 % SI on pelvic MRI

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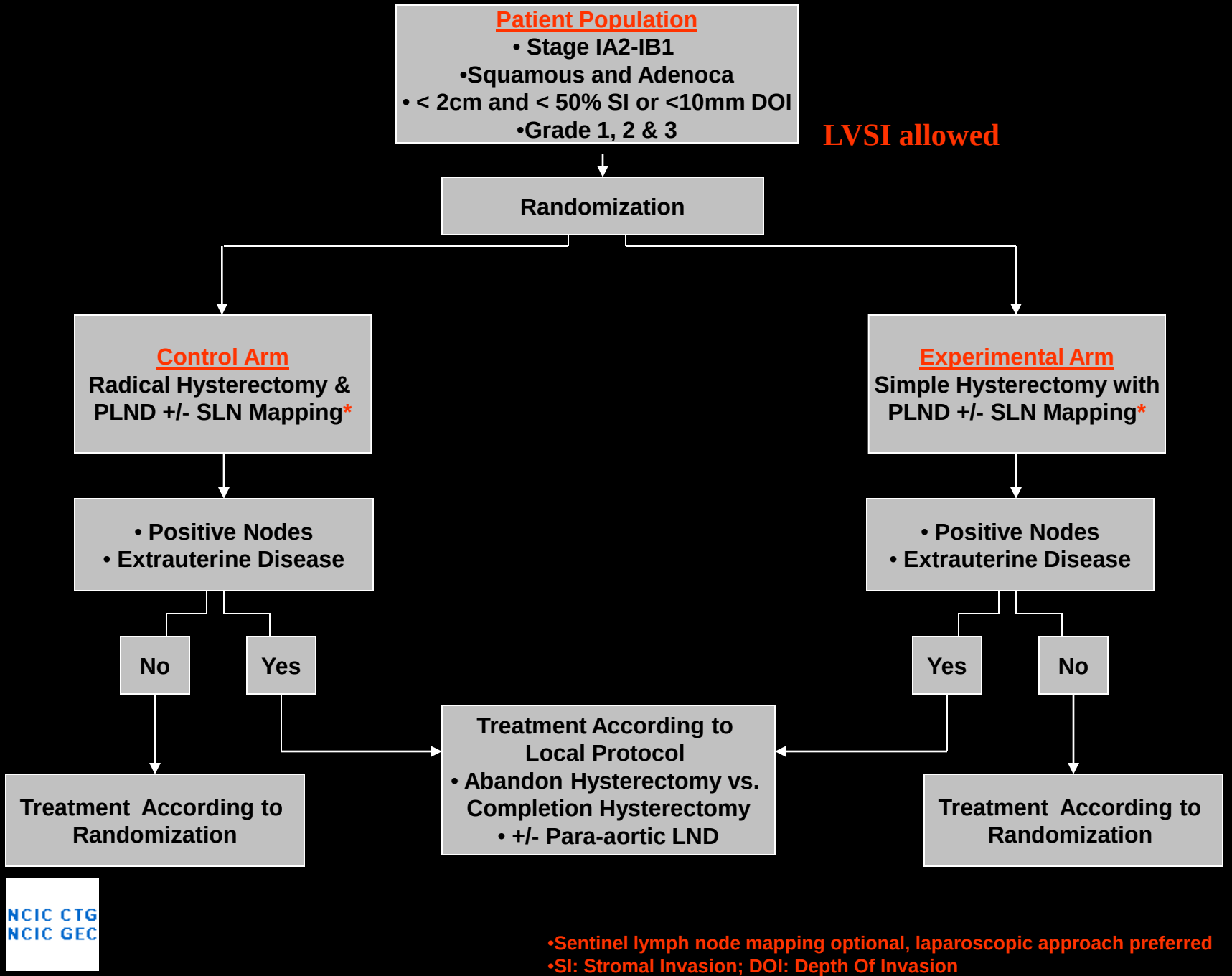
Patient Population
• Stage IA2-IB1
•Squamous and Adenoca
• < 2cm and < 50% SI or <10mm DOI
•Grade 1, 2 & 3
LVSI allowed
Randomization
Control Arm
Radical Hysterectomy & PLND +/- SLN Mapping*
Experimental Arm
Simple Hysterectomy with PLND +/- SLN Mapping*
• Positive Nodes
• Extrauterine Disease
• Positive Nodes
• Extrauterine Disease
No
Yes
Yes
No
Treatment According to Local Protocol
• Abandon Hysterectomy vs. Completion Hysterectomy
• +/- Para-aortic LND
Treatment According to Randomization
Treatment According to Randomization
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•Sentinel lymph node mapping optional, laparoscopic approach preferred
•SI: Stromal Invasion; DOI: Depth Of Invasion

Exclusion criteria

Exclusion criteria

- High risk histology
  - clear cell, small cell
- Stage IA1
- Evidence of lymph node metastasis or extrauterine disease (pelvic MRI)
- Neoadjuvant chemotherapy
- Pregnancy
- Desire to preserve fertility

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Stratification

- Cooperative group
- Surgical approach (Abd vs MIS)
- Stage (IA2 vs IB1)
- Histology (squamous vs adeno)
- Grade (1,2 vs 3)
- SN mapping (yes vs no)

Note: LVSI will not be included as a stratification factor but will be evaluated separately in the final data analysis

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Trial schema

Low-risk cervical cancer as defined by:

- Stage IA2-IB1 squamous cell, adenocarcinoma/adenosquamous carcinoma
- < 2cm, at least 3mm of intact cervical stroma and < 50% stromal invasion
- Grade 1-3

RANDOMIZE

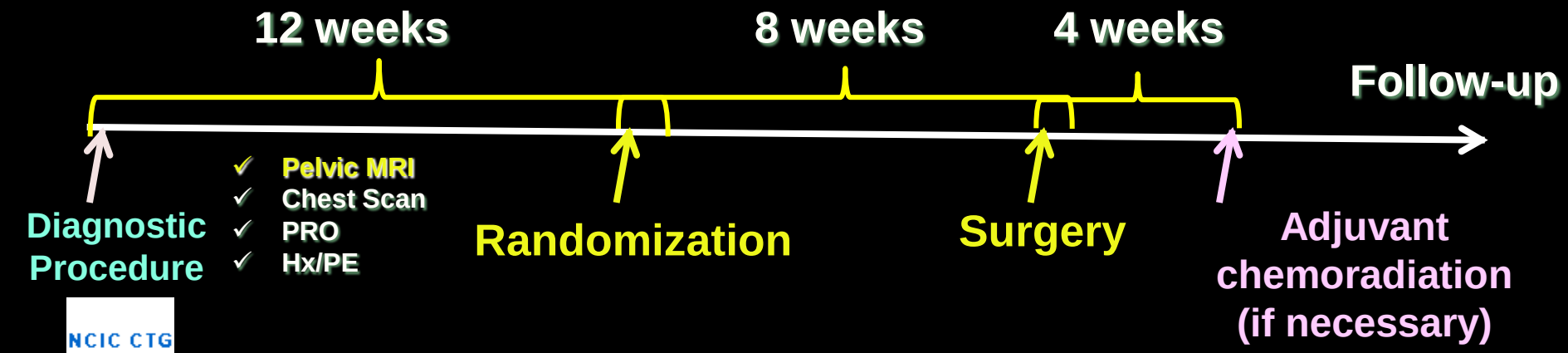
↗ ARM 1 (Control)
Radical Hysterectomy*

↘ Arm 2 (Experimental)
Simple Hysterectomy*

→→ Pelvic relapse

* Regardless of treatment assignment, surgery will include pelvic lymph node dissection with optional sentinel lymph node (SN) mapping. If SN mapping is to be done, the mode is optional, but the laparoscopic approach is preferred.

Planned sample size: 700 (non-inferiority at 0.05 level with 80% power)



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Objectives

- **Primary trial objective:**
  - To show that **simple hysterectomy** in low risk cervix cancer patients is **safe** and is associated with **less morbidity** than radical surgery
  - To show that **overall survival** will not be significantly different between rad hyst and simple hyst

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Trial Endpoints

Primary endpoint

- Pelvic relapse-free survival (PRFS)

Secondary endpoints

- Treatment-related toxicity
- Extrapelvic relapse-free survival
- Overall survival
- Rate of sentinel node detection
- Rate of + parametria, margins, and pelvic node
- Patient Reported Outcome (PRO)
  - Quality of life (including measures of sexual health)
  - Cost effectiveness and cost utility

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NCIC-CTG early cervix trial

Trial Design

- 1:1 multicenter prospective randomized trial
- Non-inferiority trial design at 0.05 level with 80% power
- Sample size : 700 patients

Duration of the study

- 3.5 years for accrual (200 ptes/year)
- 3.5 years of follow-up
- Total duration: 7.0 years

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Treatment plan

- **Radical Hysterectomy- Type II**

The uterus, cervix, medial 1/3 of parametria, 2 cm of the uterosacral ligaments and upper 2 cm of the vagina are to be removed *en bloc*.

- **Simple Hysterectomy**

The uterus with cervix but without adjacent parametria and a max of 0.5 cm of vaginal cuff

Procedure can be performed abdominally, laparoscopically, robotically or vaginally.

Treatment plan

- **Lymphadenectomy**
  - **Pelvic (mandatory)**
  - **Para-aortic (as required)**
  - **Sentinel Node Mapping (based upon previous credentialing)**

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Adjuvant treatment

- **Adjuvant Therapy**
  - **Most patients will not require adjuvant Tx**
  - **If there is evidence of intermediate or high risk features on final pathology, then patients will have adjuvant therapy**

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SHAPE

- Has received **CIHR grant** (2.2 millions)
  - In effect, April 1st 2012, for a total of 8 years
- Will cover
  - **Central office cost** to conduct the trial
    - Regulatory, data management, IT support, stats, etc
  - **Canadian per case funding**
- Each cooperative group is responsible for securing its own funding

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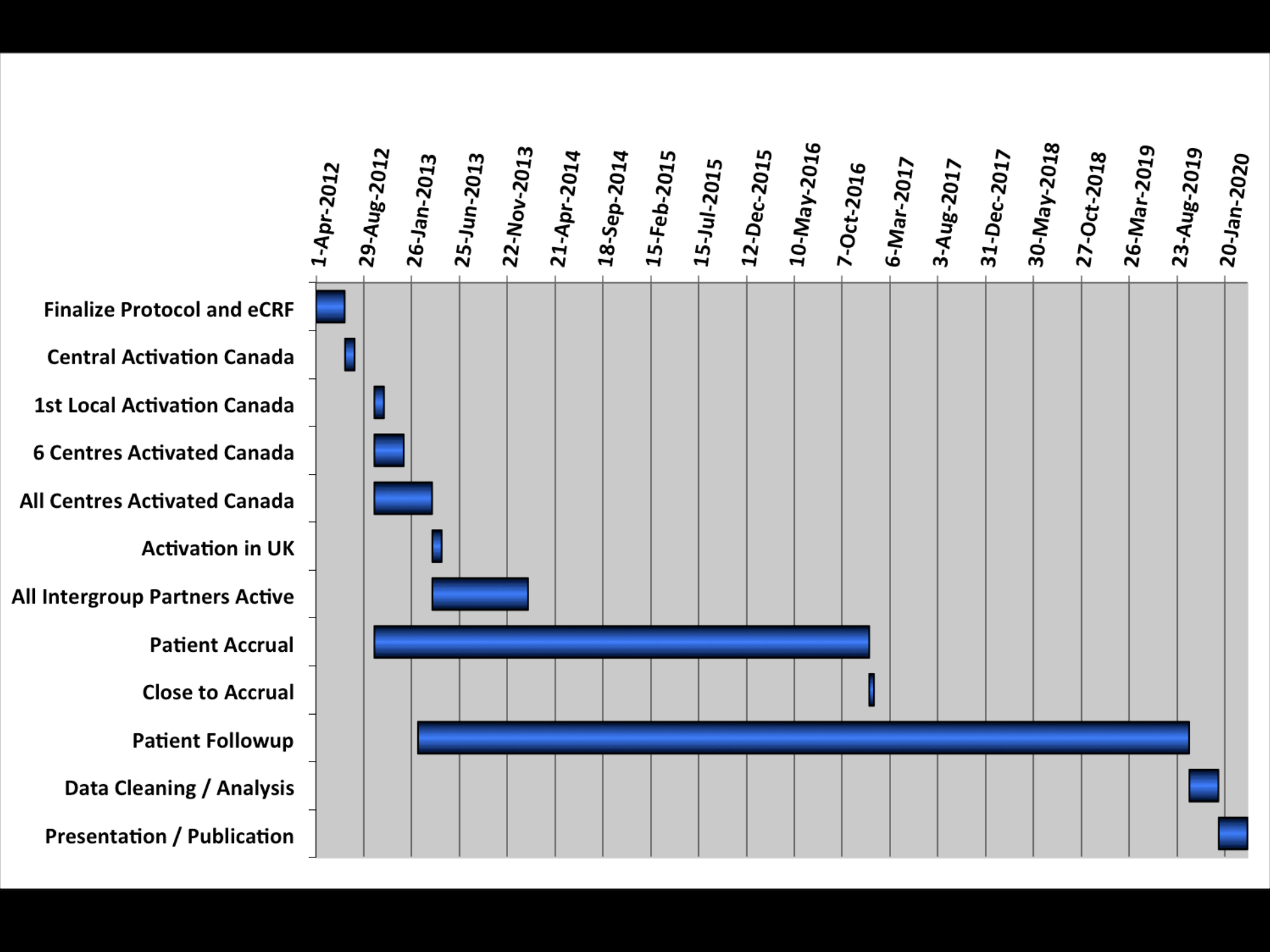
1-Apr-2012
29-Aug-2012
26-Jan-2013
25-Jun-2013
22-Nov-2013
21-Apr-2014
18-Sep-2014
15-Feb-2015
15-Jul-2015
12-Dec-2015
10-May-2016
7-Oct-2016
6-Mar-2017
3-Aug-2017
31-Dec-2017
30-May-2018
27-Oct-2018
26-Mar-2019
23-Aug-2019
20-Jan-2020
Finalize Protocol and eCRF
Central Activation Canada
1st Local Activation Canada
6 Centres Activated Canada
All Centres Activated Canada
Activation in UK
All Intergroup Partners Active
Patient Accrual
Close to Accrual
Patient Followup
Data Cleaning / Analysis
Presentation / Publication