

# Combining Patient and Research Priorities: Lessons Learned in a Community Research Collaboration Design of a Clinical Trial

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# Introduction

- About 1/3 of new cases of invasive breast cancer in the U.S. occur in women under the age of 50
- The majority of young women with early stage breast cancer will receive adjuvant chemotherapy
- Decreased fertility as well as permanent menopause are known complications of adjuvant chemotherapy that increase with age
  - The extent of this complication is unknown, but ranges from 20-100%
  - Highly dependent on age at treatment, with age  $\geq 35$  a significant risk factor
  - Early menopause is associated with multiple side effects that reduce quality of life
- Is this a necessary and unavoidable side effect of treatment directed toward cure from breast cancer?

# Background

- Patients report a lack of information on this effect at diagnosis
  - Referral to fertility specialists rare, many MDs biased against fertility preservation
- Prior data in lymphoma patients suggests that chemical ovarian suppression with GnRH agonists may protect the ovaries from chemotherapy related damage

<b>Lymphoma</b>	<b>GnRH/Chemo</b>	<b>Chemo</b>
<b># patients</b>	<b>55</b>	<b>55</b>
<b>Age</b>	<b>15-40</b>	<b>14-40</b>
<b>Menses</b>	<b>94%</b>	<b>44%</b>
<b>Pregnancies</b>	<b>18 in 12 women</b>	<b>13 in 8 women</b>
<b>Ovarian failure</b>	<b>6%</b>	<b>56%</b>

# Background (2)

- Two reported breast cancer studies – no data on estradiol levels, quality of life, variable timing of the start of ovarian suppression
  - Pecchia et al, 2002
    - 64 patients, median F/U 55 months, 86% recovered menses; one had a successful pregnancy
      - No data on estradiol, quality of life, or number of patients who desired pregnancy
  - Fox et al, 2003
    - 24 patients, median age 35, low dose lupron given anywhere from 2 weeks before to day of chemotherapy
      - Amenorrhea only by cycle 3, menses resumed in 23/24 by 12 months
      - 6 pregnancies in 5 patients; 3 required fertility treatment, 2 live births
      - 3 patients unsuccessful despite fertility treatments
    - Preservation of fertility in this population still unclear
- Pregnancy following a breast cancer diagnosis appears to be safe
- Chemotherapy induced menopause has unclear benefits on disease free survival combined with current adjuvant treatment strategies

# Community Research Collaboration (CRC) Grants

- Communities should actively participate in research about issues that concern them.
- Established in 1997
  - Require a partnership between community members and experience research scientists
  - Goal is to work together to identify the research question, develop the research plan, carry out the research, interpret the results, and disseminate information to the community
- 24 funded to date, 13 pilot and 11 full awards
  - This is the first funded clinical trial, and the first trial with both a clinical treatment and qualitative component

# TIME LINE FOR DEVELOPMENT OF THE COMMUNITY RESEARCH COLLABORATION

Community Collaborator (LB) discusses possibility of clinical trials in this area with CBCRP, CRC mechanism suggested.

LB submits a CRC concept paper for a neoadjuvant trial of chemotherapy with ovarian protection to the CBCRP

1990's

10/00

11/00

12/00

Community Collaborator has personal experience with breast cancer in her 30's, is frustrated by lack of information and counseling on fertility risks as well as lack of support for child-bearing in breast cancer survivors.

Positive feedback from W. Price, LB needs to find Co-PIs, contacts 8 different MDs

Second meeting with HR only 8 weeks from CRC deadline  
Need to present project to UC Breast Cancer Site Committee  
LB goals very broad and include  
use of novel experimental ovarian antagonist,  
treatment in the neoadjuvant setting,  
use of aromatase inhibitors; HR still very unsure of feasibility

LB meets fertility specialist at Stanford,  
LW signs on to participate  
4 weeks from CRC deadline LB and  
HR still not clear on who is doing what,  
where antagonist might come from,  
hormonal therapy, neoadjuvant setting

12/00

1/01

2/01

3/01

LB contacts oncologist (HR) at UCSF  
Initial skepticism about ability to do  
study with pilot CRC budget and grant  
submission deadline of 10 weeks;  
CBCRP suggests 3<sup>rd</sup> Co-PI in gyn

After initial writing, child vacation conflicts for all  
three PI's, lack of consensus and budget,  
decision by LB made to not submit this year –  
HR realizes she should have  
said this weeks ago. General discomfort in  
communications on all sides, not clear  
If working relationship will survive

# Research Goals

- Important to address needs of community and issues associated with logistics of a clinical trial
  - Community collaborator (CC) brings personal experience and research, many ideas from survivors in her community
  - Academic oncologist (AO) concerned about feasibility, far-reaching goals, use of an experimental agent for ovarian suppression, budget, overlap with other trials, ability to achieve multiple goals with a single primary research aim
  - Fertility specialist counseled that participation ‘not worthwhile for academic career’; AO counseled in similar way.
  - CC concerned that community interests would be overlooked; has strong opinions based on her own research
- Struggle with randomization issue!

# Solution!

- Developed two pronged research plan including
  - A prospective phase II clinical trial with quality of life component
  - A retrospective assessment of patient's views of the impact of fertility on treatment choices, acceptance of randomized clinical trial on this treatment
- Allowed significant input and creativity on both the CC and AO part, with consultation from the fertility specialist on both aspects

LB reforms team. Extensive negotiations of study plan.  
Decision to submit concept paper

Novel approach decided for concept paper submission. Two components to meet research goals: simple Phase II clinical trial, qualitative study to assess women's attitudes

5/01

9/01

11/01

12/01

LB talks with other docs at UCSF about the trial, presents idea at Breast Cancer Program Protocol Review Committee.  
Feedback: restart the original team and make it work! Simplify the concept to avoid overlap with other studies and unfeasible/conflicting goals.

Feedback from CRC review: Finalize design, pharmaceutical commitment, ?need for formal community organization involvement?  
Otherwise strong encouragement.

**LB's dilemma:** Satisfy original goals and research interests while making the study work with collaborators who are essential to the success of the trial. Address community concerns and interests. Balance work and family!

**HR's dilemma:** Make sure the project is scientifically and clinically feasible and worthwhile from an academic career standpoint without stepping on LB's plans and research goals. Balance work-load so this project can get enough time and effort

# Novel Aspect of Trial Design

- Two research aims that involve both a qualitative and clinical trial component
  - Utilizes skills of all collaborators
- Three female PIs
  - One CC, two academic physicians at different academic centers
  - All married, with children, extended family responsibilities and working husbands!

# Primary Aims of Research Collaboration

- Will ovarian suppression started before chemotherapy result in a lower risk of amenorrhea within 6 to 9 months after end of treatment than what is reported with chemotherapy alone?
- What is the feasibility of this trial design?
- What are the key factors such as demographics, cancer biologic factors, and personal/lifestyle issues that influence a woman's attitude toward ovarian toxicity from alkylating chemotherapy? How do these factors influence a woman's interest in a randomized trial evaluating agents that may preserve ovarian function?

# Initial Stumbling Blocks

- Process of establishing co-investigators
  - Determining roles
  - Finding a middle ground on study design, non-unilateral decision making
  - Conflict resolution
- Collaboration on grant writing
  - Funding considerations
    - Need for additional pharmaceutical support
    - Where to have primary funds given two institutions
    - How to fund salary of community collaborator
      - Under which Co-PI? Which institution?

# Schema of Clinical Trial

## Eligibility Criteria

- Women aged 35-44 for whom adjuvant chemotherapy is planned
  - Stage I-IIIa cancer, any ER/PgR.
  - Regular menses, 21-35 day cycle
    - Not pregnant
  - No prior chemotherapy



## **Single-arm Phase II trial**

Pilot nature precludes stratification.

- Age-based quota sampling:  
Maximum 8 women aged 42-44

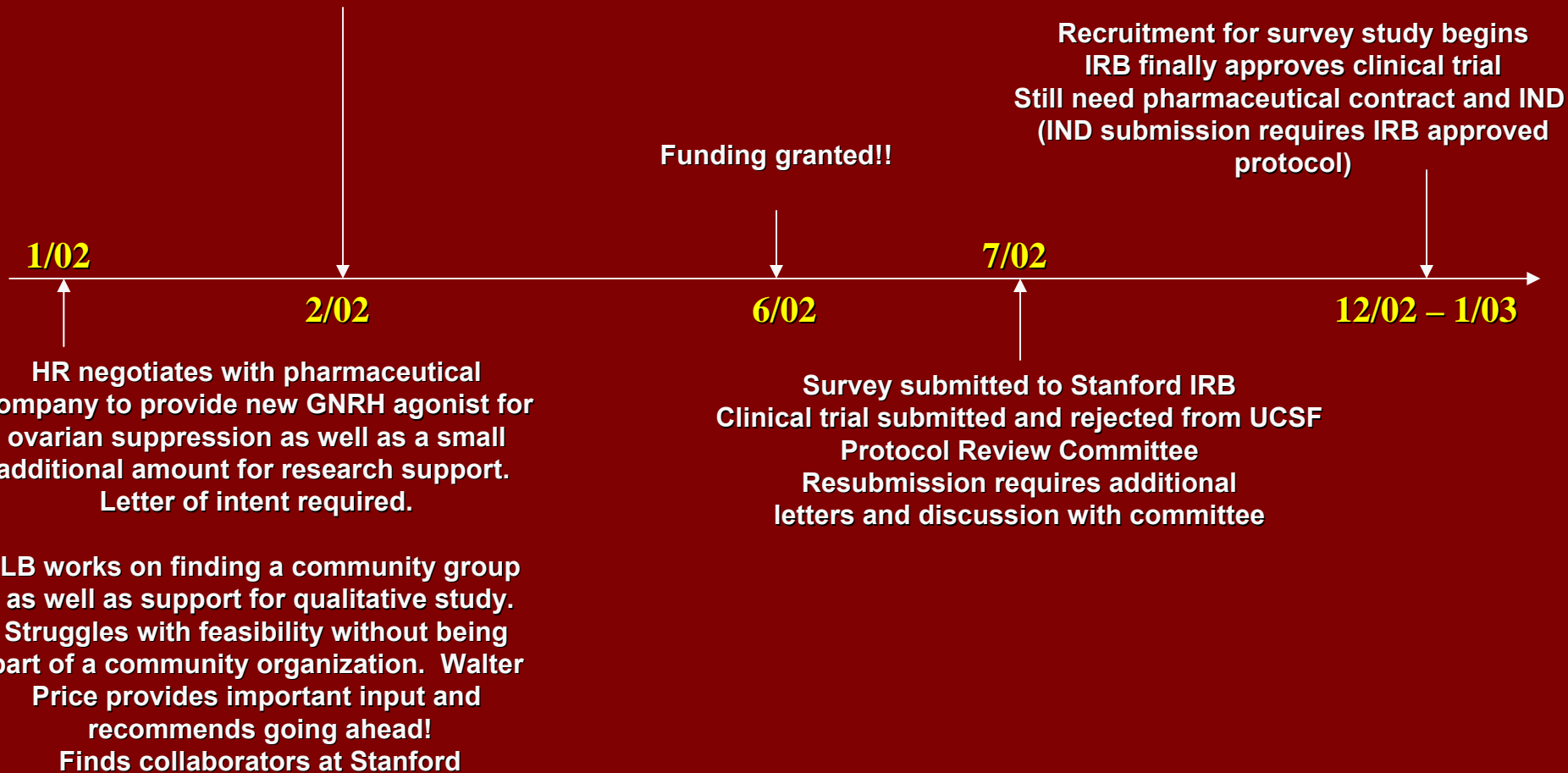


Begin ovarian suppression with GNRH agonist at least 2 weeks before chemotherapy begins  
Continue ovarian suppression through chemotherapy course  
Monitor estradiol, quality of life throughout chemotherapy



Monitor recovery of ovarian function following end of chemotherapy  
Separate substudy: Measure antral follicle counts to better understand ovarian reserve.

Writing grant with continuous email communication  
Difficulty with Mac to PC and back emailing  
Grant submitted through both UCSF and Stanford  
3 Co-Pis. Last minute letter of support obtained  
from pharmaceutical company, and from  
community physicians. Many discussions on budget.



# Once Grant was Approved....

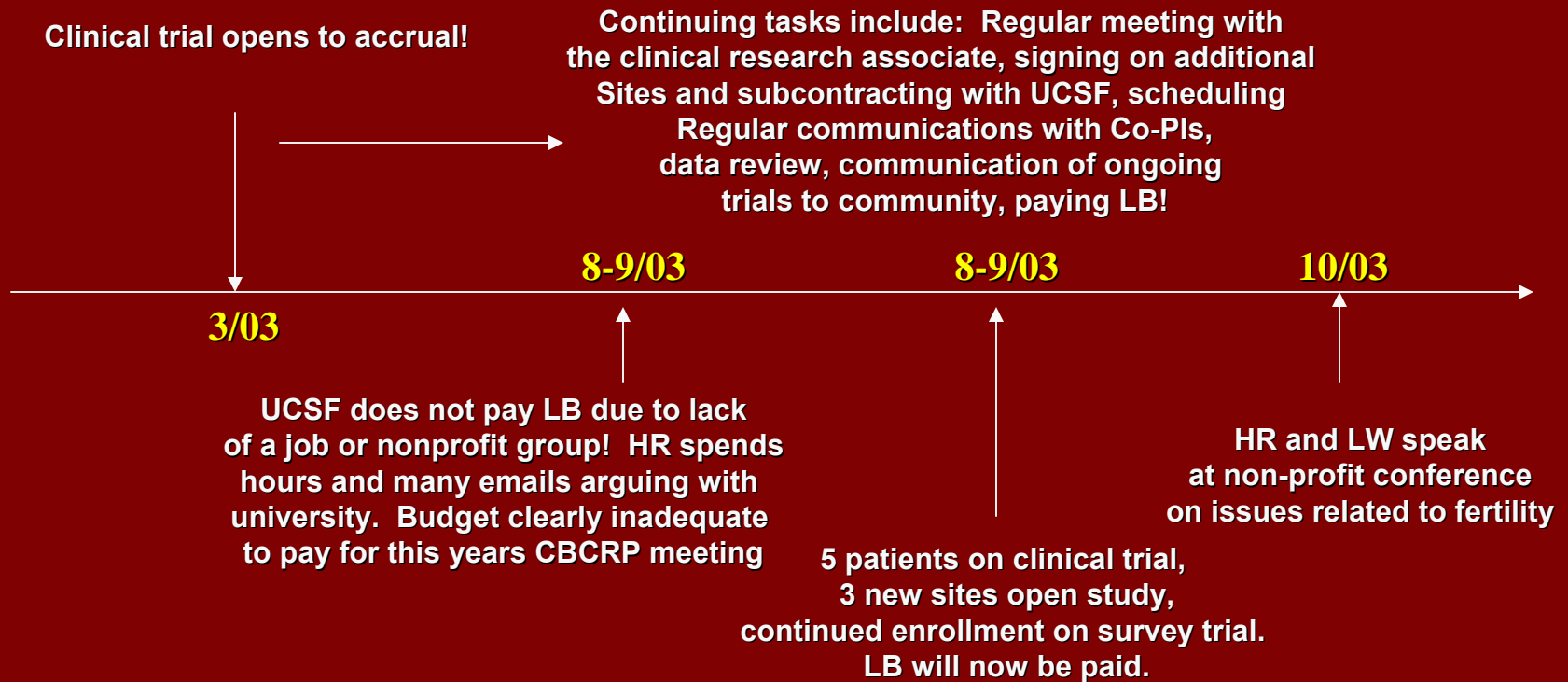
- IRB approval time-line
  - Site Committee
  - Protocol Review Committee
  - IRB
- Communication with pharmaceutical company
  - Budget and contract
- Need for IND exemption for GnRH agonist (agent to suppress ovaries)
- Getting collaborators on board

# IRB Concerns

- Should all premenopausal women with hormone positive disease go into menopause as a treatment for their cancer?
  - Response:
    - There is no data as yet to suggest that menopause provides additional benefit over anthracycline-based chemotherapy followed by tamoxifen in this patient population. Planned randomized trials will address this research question
    - Given the lack of data, it would be inappropriate to limit the study population to women with hormone receptor negative disease; women should be given the opportunity to participate in decisions regarding their own fertility.
- Inform women that preservation of fertility may have adverse effects on outcome
  - Response
    - There is no data to suggest an adverse outcome with current chemotherapy regimens; patients will be informed that this is unknown and the potential for risk exists.

# Ongoing Issues

- Communication between Co-Pis – there is not enough!
  - Stumbling blocks:
    - Geography
    - Work!
    - Childcare/family
  - What has worked for us?
    - Frequent email communication (we all check daily)
    - Conference calls set up through UCSF (free)
- Data review
  - Through email, phone conferences
  - So far is working well
- Communication with community
  - Primarily through community collaborator so far
  - More work on this in second year planned
- Recruitment to both trials
  - Collaborative efforts ongoing to:
    - Add sites for clinical trial
    - Increase community awareness



# Conclusions

- Community collaboration in both clinical and qualitative trials is feasible and important
  - Community input is critical to identify important and less visible patient issues for clinical research
  - Input in both study design and conduct by breast cancer survivors is important to success of research effort
  - In our grant, the collaboration strengthened the research plan in several ways:
    - Establish MD collaborators to allow patients to be treated locally on this trial
    - Obtain data from the survey on preferences that will provide important data for the next protocol design
- Clinical trials pose additional challenges in Community Research Collaboration grants
  - The 18 month time line for pilot grants is short for clinical trials
- Continued effort and funding is necessary to ensure success of this important initiative

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