PREGNANCY OUTCOME AND SAFETY OF INTERRUPTING THERAPY FOR WOMEN WITH ENDOCRINE RESPONSIVE BC

IBCSG 48-14 / BIG 8-13
A221405

POSITIVE TRIAL

OVERVIEW

ANN H. PARTRIDGE
NORTH AMERICAN PI
5/12/16

BIG Breast International Group
ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY
SAKK
NABCG The North American Breast Cancer Group
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BACKGROUND

- About **15%** of patients with BC are diagnosed **during** their **reproductive years.**
- In the last decades **women tend to delay childbearing** for different reasons (i.e. cultural, educational, professional)
- In an increasing number of patients **BC occurs before the completion of their reproductive plans**.
- **5-10 years of ET may substantially reduce** the chance of a **successful conception**.
- A **shorter duration** of ET in this population **has not been studied** in a prospective manner.

BACKGROUND

- **Pregnancy after BC does not seem to increase the risk of relapse**.
- In a multicenter, retrospective cohort study, **no difference in DFS** was observed **between pregnant and non-pregnant** patients in the ER+ population.
- In the same analysis, **no difference in DFS** was observed between **patients who became pregnant <2 years** following BC diagnosis and those who became pregnant afterwards.
- **Birth outcome** after BC is apparently **not different** from the general population.
- The **limited evidence available on breastfeeding reports successful lactation from the treated breast in ~ 30%** of women without detrimental effect on survival.

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Rationale for the Positive Trial

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POSITIVE SCHEMA

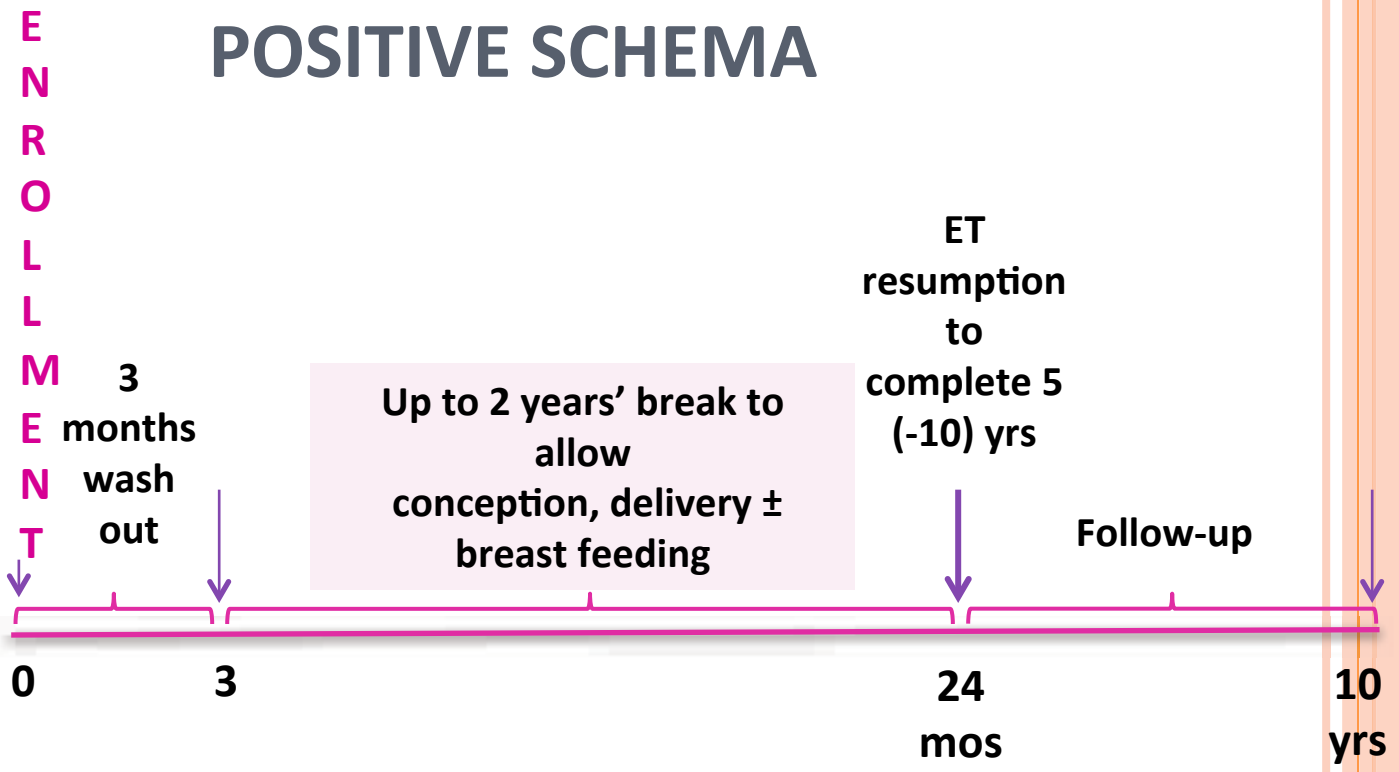
Screening/eligibility:

Patients with **ER+** early breast cancer

≥ 18 and ≤42 years at enrollment

Completing 18-30 months of ET (SERMs alone, GnRH analogue + SERM or AIs) [1]

Pregnancy desire



[1] *± CT*

[2] *No more than 1 month prior enroll.*

Translational research

- Ovarian function evaluation
- Uterine evaluation
- Circulating tumor DNA (ctDNA)
- Genomic evaluation of primary breast tumor

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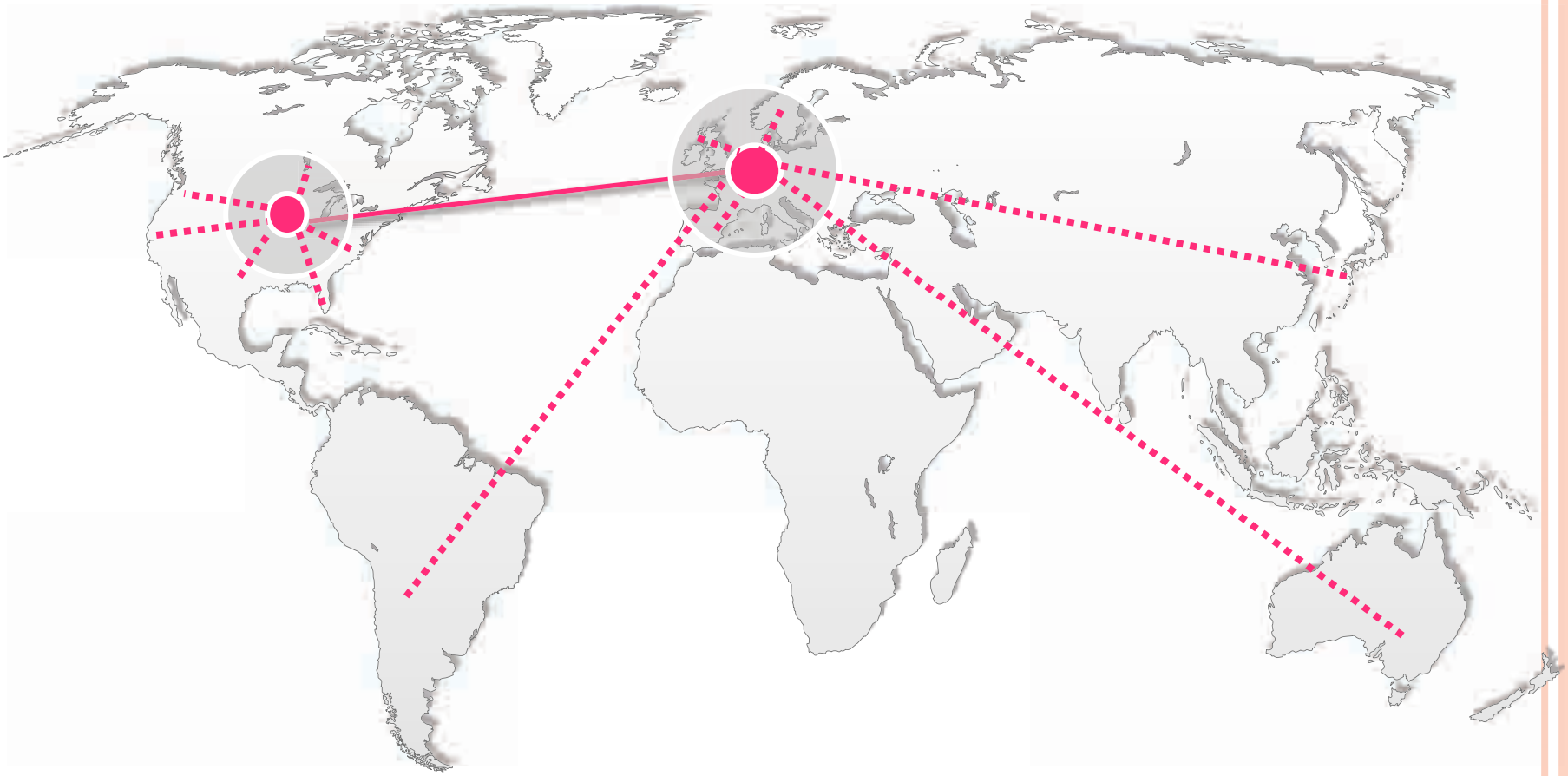
Translational Research
Central Labs → Brussels, Belgium

Central Lab for Ovarian Function Analysis:
Free University of Brussels
Isabelle Demeestere
Research Laboratory on Human Reproduction

Central Lab for Circulating Tumor DNA Analysis:
Institut Jules Bordet
Michail Ignatiadis
Breast Cancer Translational Research Laboratory



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North American Sites
→ Mayo Clinic, Rochester, MN

Central Lab in North America
→ Mayo Clinic, Rochester, MN

1. **To distribute kits to N.A. sites**

2. **Collect blood and FFPE samples from N. A. sites**

3. **Batch material to transfer:**
   Fluids to Brussels, Belgium, and
   FFPE to Milan, Italy

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Blood Collection Kits

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Blood draws timelines: CENTRAL evaluation

Time point	Ovarian Function Serum Sample (AMH, FSH, E2)	Serum Progesterone	Circulating Tumor DNA (ctDNA) (Plasma)
Enrollment			10 ml in EDTA tube
Month 3, day 2-5 of the menstrual cycle or anytime if amenorrhea	10 ml in serum collection tubes		
Month 6, between day 21 – Day 25 (if patient is not pregnant at this time point)		(only for patients with active menstruation) 5 ml in serum collection tubes	10 ml in EDTA tube
Month 12, day 2-5 of the menstrual cycle or anytime if amenorrhea (if patient is not pregnant at this time point)	10 ml in serum collection tubes		
3-6 months after resumption of ET			10 ml in EDTA tube
Second trimester of pregnancy			10 ml in EDTA tube
At breast cancer recurrence event			10 ml in EDTA tube

*Only for patients who become pregnant

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BLOOD DRAWS TIMELINES: LOCAL EVALUATION

TIME POINT	SERUM PRL	SERUM TSH
3 MONTHS	ANALYSIS OF **PRL** AND **TSH** WILL BE DONE LOCALLY IN REAL TIME RESULTS TO BE REPORTED ON THE PATIENT eCRF	
12 MONTHS (ONLY IF THEY WERE ABNORMAL AT 3 MONTHS AND NO PREGNANCY OCCURRED)		

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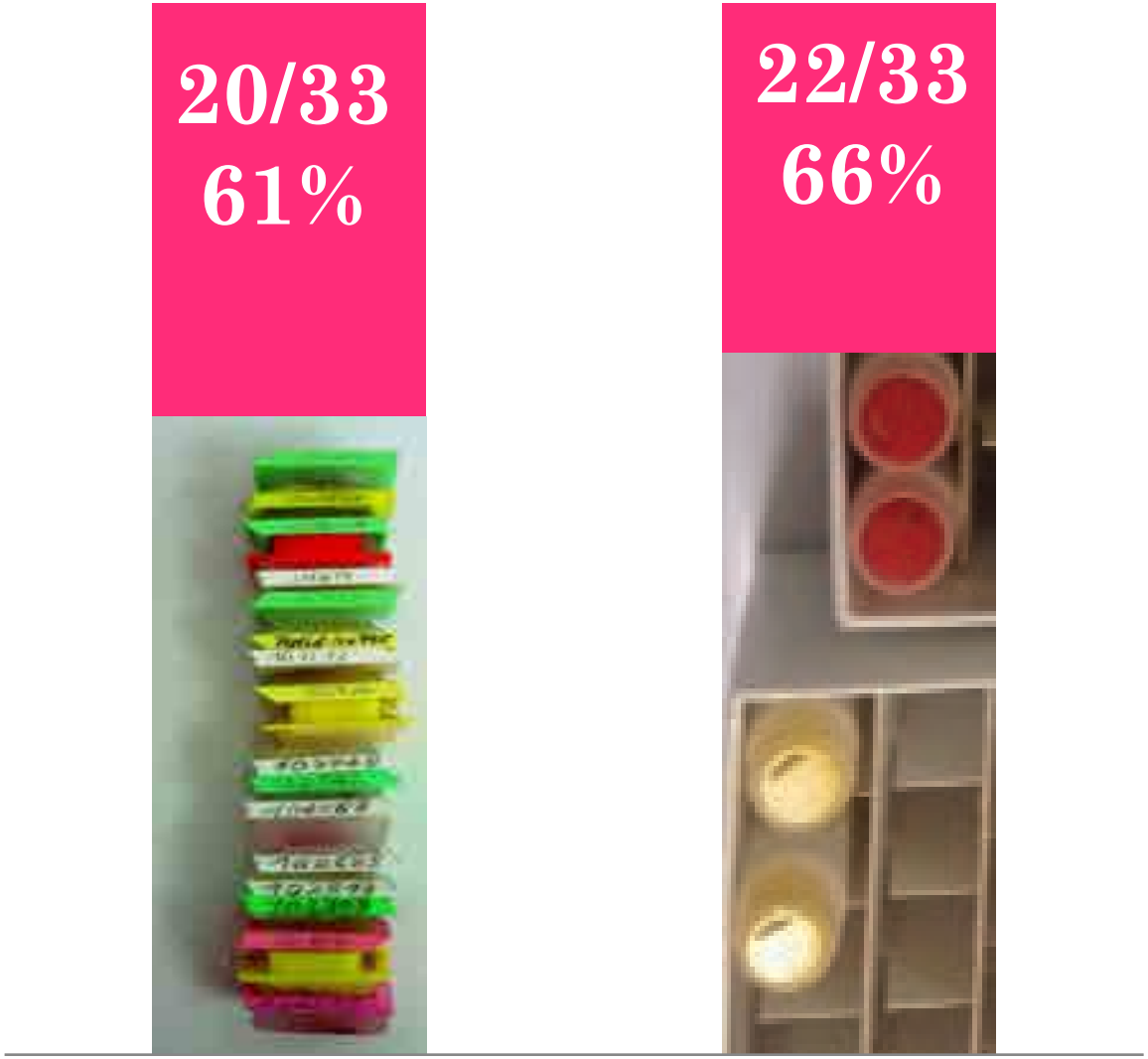
20/33
61%
22/33
66%
FFPE Primary Tumor
Month 3 Serum

FFPE Pathology Submission

FFPE tumor block for central pathology review and banking (**at least 5mm invasive tumor and a minor component of normal breast tiss**ue).

Please notify the pathologist of this requirement in advance.

Slides are NOT an alternative→ loose antigenicity

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Central Pathology Review
Banking for Translational Research

Central Pathology Review – evaluation by a board-certified pathologist, quality control of at least 10% of the cases by a second board-certified pathologist.

ER, PgR by IHC
Ki-67 labeling index by IHC
HER2 by IHC; confirmed by FISH

IBCSG Central Pathology Office
European Institute of Oncology
Milan, Italy

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FFPE BLOCK OF PRIMARY TUMOR (FROM SURGERY)

Aim: Elucidate the biology of BC in young women and also the factors associated with sensitivity/resistance to ET.

IHC, in situ hybridization, expression profiling and sequencing. Extraction of nucleic acids (DNA and RNA) may be required to perform these analyses

- **Central Pathology assessment on the primary tumor is mandatory, but patients will be evaluated for eligibility according to tumor characteristics as determined by the local pathologist.**
- The work of the pathologist is basic to the success of all studies. Each Participating Center should identify a pathologist responsible for study patients.

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FFPE Block Payment / Shipment

100 Euro/USD is provided by IBCSG for the work associated to submit the FFPE tumor block.

Transferred upon:

- receipt of the block at the IBCSG CPO.

An IBCSG DHL/FedEx account may be used to transfer the FFPE blocks.

Questions:

IBCSG Translational Research Coordinator
Rosita.Kammler@ibcsg.org

IBCSG 48-14 / BIG 8-13
ALLIANCE # A221405
POSITIVE TRIAL

LEARNING CHECKS

INVESTIGATOR MEETING

IBCSG ANNUAL MEETING
AMSTERDAM, 12 MARCH 2016

First year trial conduct - Learning Checks
ELIGIBILITY CRITERIA

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ELIGIBILITY CRITERIA

- Has received adjuvant ET (SERM alone, GnRH analogue plus SERM or AI) for **≥18 months but ≤30 months** for early breast cancer

- ☞ Patient started **LHRH analogue together with adjuvant CT**.
- ☞ She started **TAM 6 months later.**
- ☞ **18 months after LHRH start** she wants to **interrupt ET to get pregnant**.

Only 12 months of TAM !?!

ELIGIBLE !

ELIGIBILITY CRITERIA

- Adjuvant **ET must have stopped within 1 month prior to enrollment**

  month 0 = date of ET interruption

She **interrupted ET 2 months ago after 30 months** because she wanted a baby

NOT ELIGIBLE

She **interrupted ET 15 days ago after 18 months** because she wanted a baby

ELIGIBLE - register the patient within 15 days!

She started **ET 12 months ago but now she wants a baby**

NOT ELIGIBLE NOW - WAIT 6 months!

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ELIGIBILITY CRITERIA

- **Patient must be ACCESSIBLE for follow up**

ELIGIBILITY CRITERIA!

Do **not enroll patients unable to come to your site** for visits and/or patients with a history of noncompliance

- **TR blood samples for central evaluation!**
- Menstruation recovery, pregnancy and offspring data collection.

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PATIENT MANAGEMENT

Resumption of menses and conception depends on patient's age and adjuvant treatment received.

The 2 year interruption period is approximate!

Can patients get pregnant after 23 months from ET interruption?

Yes!

The patient will restart ET after delivery and breastfeeding (if feasible and desired)

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PATIENT MANAGEMENT

- **Patients must be advised** to use effective non hormone-containing **contraception or be abstinent for 3 months after ET interruption** (NOT enrollment) before attempting conception.

to be reported promptly to the IBCSG
by submitting the **Pregnancy Form** (48-PREG)

Patient will not be excluded from the trial and will be followed as per protocol

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PATIENT MANAGEMENT

What if a patient does not succeed in getting pregnant within 24 months after ET interruption, decides not to resume ET and becomes pregnant later on?

Patient will not be excluded from the trial and will be followed as per protocol

And should TR assessments be performed?

YES, plasma for ctDNA must be taken the second trimester of pregnancy, 3-6 months after ET resumption (if she restarts ET) and at relapse (if this occurs)

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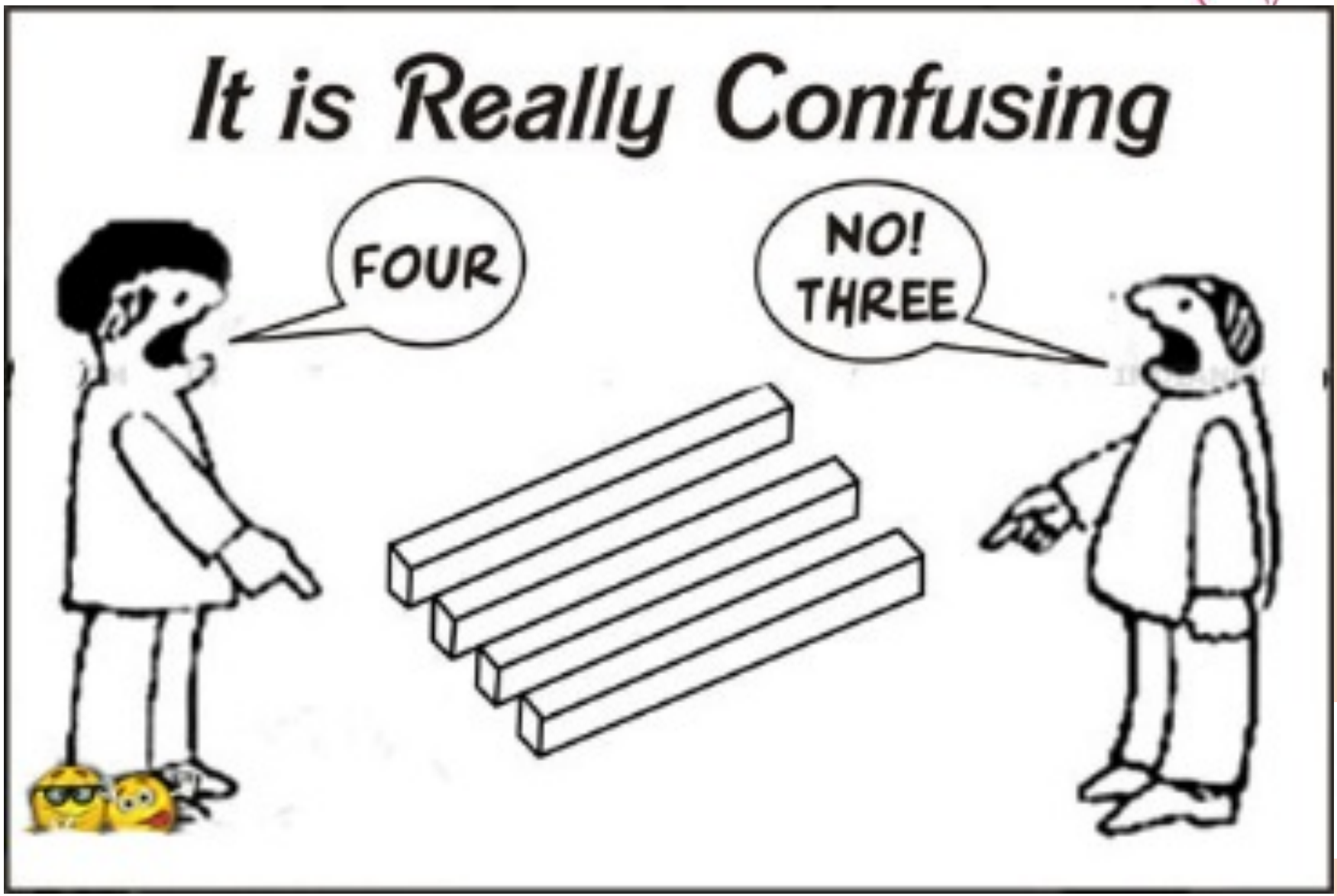
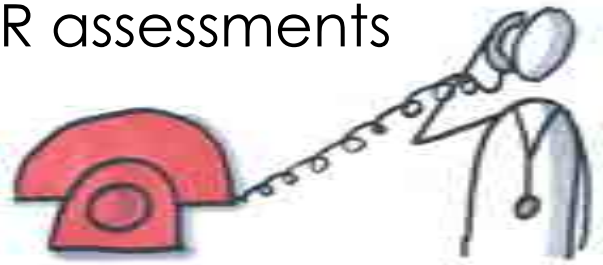
Translational Research

Assessments Time Points



TR ASSESSMENTS TIME POINTS

- Some blood draws **time points depend strictly on recovery of menses.**
- **Recommend patients to contact you as soon as they recover menses** to carefully plan TR assessments



- Since ET must have stopped within 1 month prior to enrollment, **registration and ET interruption may not always occur in the same date**. **Visits and TR assessments need to be planned** according to the trial schedule **from ET interruption** (NOT from enrollment)

Visits and TR assessments PLANNER available on the **IBCSG or CTSU websites**.

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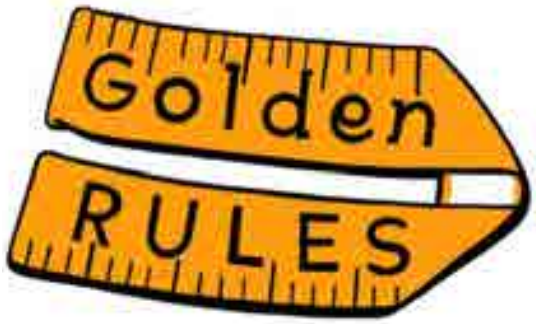
TR ASSESSMENTS TIME POINTS



1. **Take the 3M serum for ovarian function on days 2-5 of the menstrual cycle that is closer to the 3M time point, either before or after.** The same applies to 6M serum progesterone on day 21-25 of the menstrual cycle.

2. **Stick to the protocol as much as possible. If not possible, take the blood samples/ perform TV US in any case.**

TR ASSESSMENTS TIME POINTS

Transavaginal US

For patients who already recovered menses, **transvaginal US at month 3 can be performed on day 2-5 of the menstrual cycle** (same day of serum for ovarian function).
The same applies to month 6 when TV US can be taken on day 21-25 of the menstrual cycle (same day of serum progesterone).

Patients (and/or gynecologists) who are **not comfortable** in performing **transvaginal US during menses**, need to **come to the hospital in different days**.

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TR ASSESSMENTS

What if a patient resumes ET before month 12 for any reason?

- **All TR assessments** from that moment to month 12 **should NOT been performed.**
- The only TR assessment that **must always be done is ctDNA 3-6 months after ET resumption** and at relapse, if this occurs.

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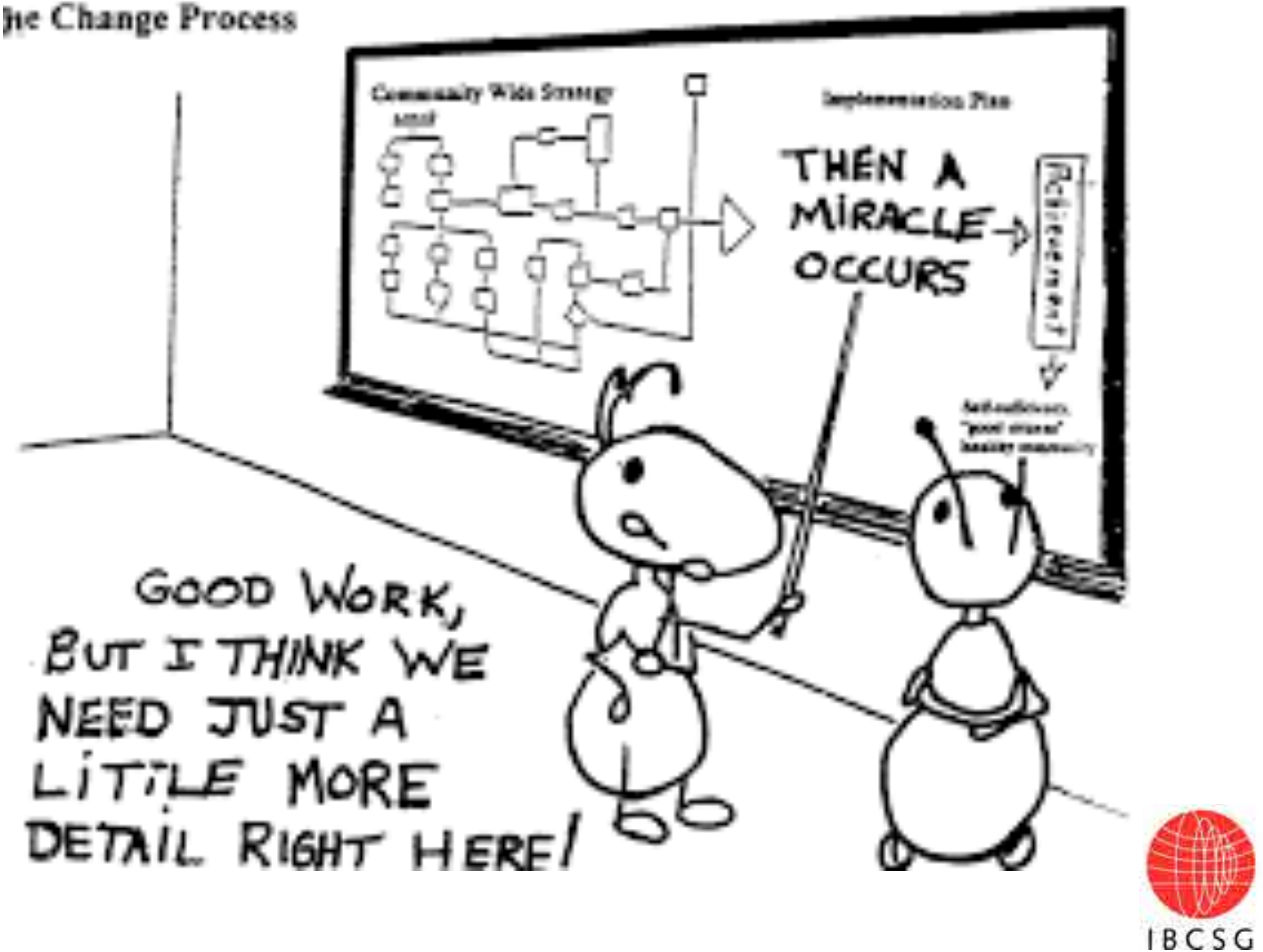
he Change Process
THEN A MIRACLE OCCURS
GOOD WORK, BUT I THINK WE NEED JUST A LITTLE MORE DETAIL RIGHT HERE!

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FAQs

http://www.ibcsg.org/Member/Clinical_Trials/Open_Trials/ibcsg_48-14_positive/Pages/FrequentlyAskedQuestionsFAQ.aspx

POSITIVE TRIAL

DATA CAPTURE AND MANAGEMENT

POSITIVE STUDY CONTACTS

IBCSG Data Management Center (DMC)
Amherst, NY,

Trial Coordinators:

- Holly Shaw (Lead TC)
- Poonam Jani

Data Managers:

- Jocelyn Swick-Jemison
- Dawn Weinbaum

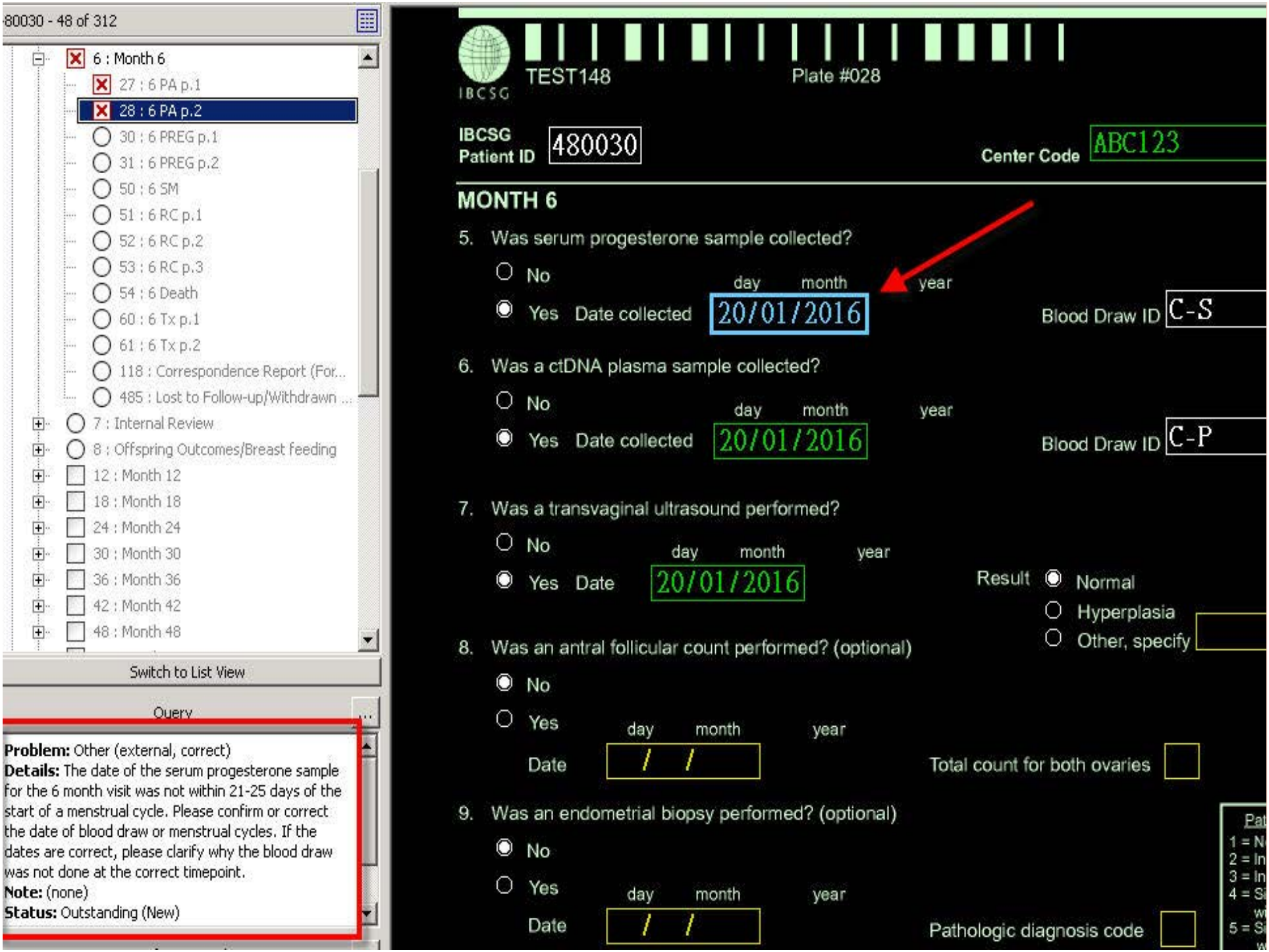
ibcsg48_POSITIVE@fstrf.org

Training and Activation

- Prior to activation, each staff member involved with POSITIVE, including the PI must be trained
- Site staff will receive a detailed trial overview and iDataFax demonstration
- Training is essential to ensure the quality of data and the efficacy of the trial

Data Collection

- Data will be entered remotely via eCRFs in iDataFax
  - Centers will be granted access to the iDataFax System and will receive training on how to submit data, resolve queries, etc.
  - CRFs are available in iDataFax 24 hours after the patient is enrolled
- Data will be managed at the IBCSG Data Management Center in Amherst, NY, USA


80030 - 48 of 312
6 : Month 6
27 : 6 PA p.1
28 : 6 PA p.2
30 : 6 PREG p.1
31 : 6 PREG p.2
50 : 6 SM
51 : 6 RC p.1
52 : 6 RC p.2
53 : 6 RC p.3
54 : 6 Death
60 : 6 Tx p.1
61 : 6 Tx p.2
118 : Correspondence Report (For...
485 : Lost to Follow-up/Withdrawn ...
7 : Internal Review
8 : Offspring Outcomes/Breast feeding
12 : Month 12
18 : Month 18
24 : Month 24
30 : Month 30
36 : Month 36
42 : Month 42
48 : Month 48
Switch to List View
Query
Problem: Other (external, correct)
Details: The date of the serum progesterone sample for the 6 month visit was not within 21-25 days of the start of a menstrual cycle. Please confirm or correct the date of blood draw or menstrual cycles. If the dates are correct, please clarify why the blood draw was not done at the correct timepoint.
Note: (none)
Status: Outstanding (New)
IBCSG
TEST148
Plate #028
IBCSG Patient ID 480030
Center Code ABC123
MONTH 6
5. Was serum progesterone sample collected?
No
Yes Date collected day month year 20/01/2016
Blood Draw ID C-S
6. Was a ctDNA plasma sample collected?
No
Yes Date collected day month year 20/01/2016
Blood Draw ID C-P
7. Was a transvaginal ultrasound performed?
No
Yes Date day month year 20/01/2016
Result Normal
Hyperplasia
Other, specify
8. Was an antral follicular count performed? (optional)
No
Yes
Date day month year / /
Total count for both ovaries
9. Was an endometrial biopsy performed? (optional)
No
Yes
Date day month year / /
Pathologic diagnosis code

FORMS NOT SUBMITTED BY iDF

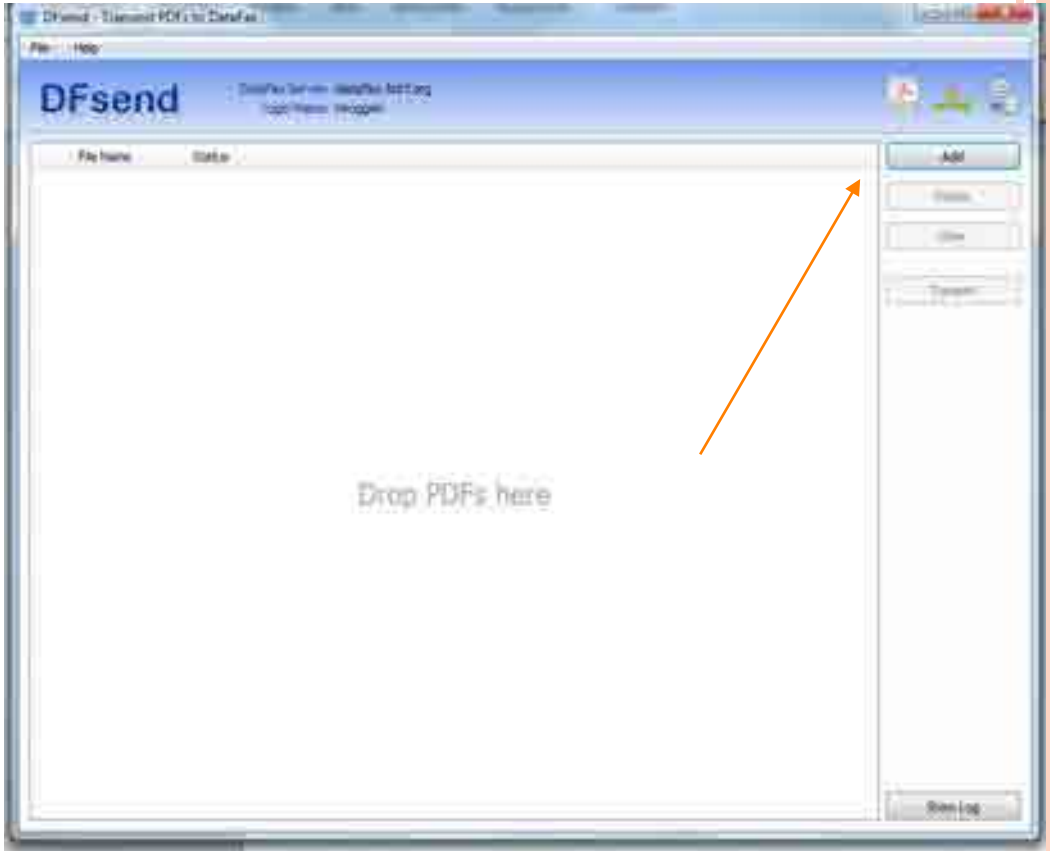
- The exceptions for data to be submitted **via DFsend or fax:**

  - **Patient completed POCS Questionnaires**
    - These forms can be printed from the IBCSG website or directly in iDataFax
    - The Confirmation of Enrollment and Assessment Checklist should be completed by the Center via iDataFax

  - **Pathology Reports**
    - Every page of the Pathology Report must have the Patient ID and Center Code
    - Pathology Report Labels are available on the IBCSG website

  - **Medical Review Queries**

DFSEND- EASY AND QUICK !!



Data Collection

- The Data Quality Control Office in Amherst, NY, USA will oversee overall data submission and query resolution metrics
- The IBCSG Coordinating Center in Bern, Switzerland will provide medical review and summary of SAEs
- The Statistical Center in Boston, MA, USA will perform the data analysis

Data Submission Timelines

- A Form and Baseline POCS Forms: due with 24 hours of patient enrollment
- H Form and Pathology Reports/HRR: due within 1 week of enrollment
- 3 Month visit and future visits are based on when the patient stopped Endocrine Therapy at or before enrollment

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Patient Menstrual Diary

- The Patient Diary will collect information on timing of menstrual recovery and on the pattern of menses
- It serves as a reminder for the patients to schedule the blood draws for translational research parameters in the designated menstrual cycles

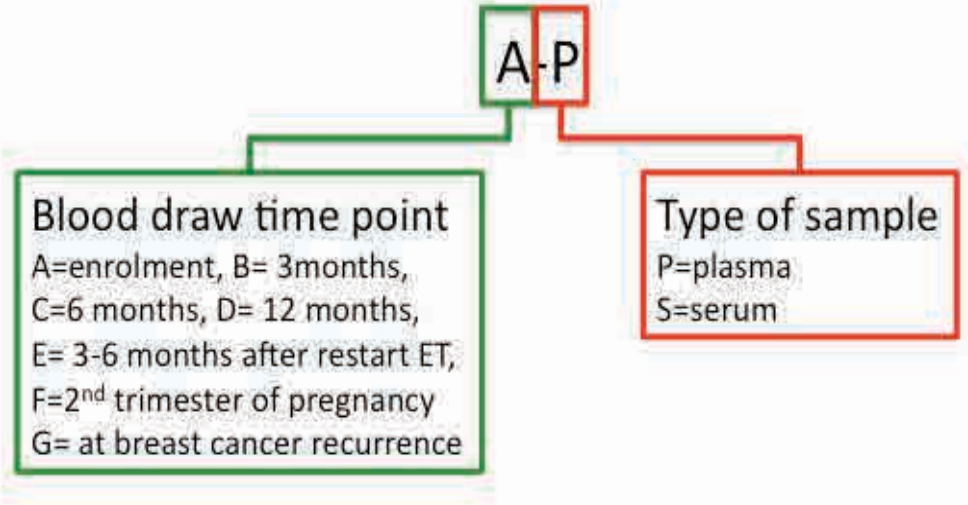
Learning Checks and Tips

Blood Draw ID

Please check the **Blood Logistics Manual** for coding the Blood Draw ID

Just two letters

NO numbers!



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TEST 148 Plate #025 Seq. # 003

IBCSG Patient ID 480013 Center Code Test2 Ver

MONTH 3 ASSESSMENT FORM (Form 48-M3A)

Instructions: This form is to be completed for all patients upon completion of the 3 month wash-out.

1. Was serum sample for central evaluation of ovarian function collected and stored?
   - ○ No
   - ◉ Yes

   Date collected (day month year) 01/03/2016

   Blood Draw ID B-S

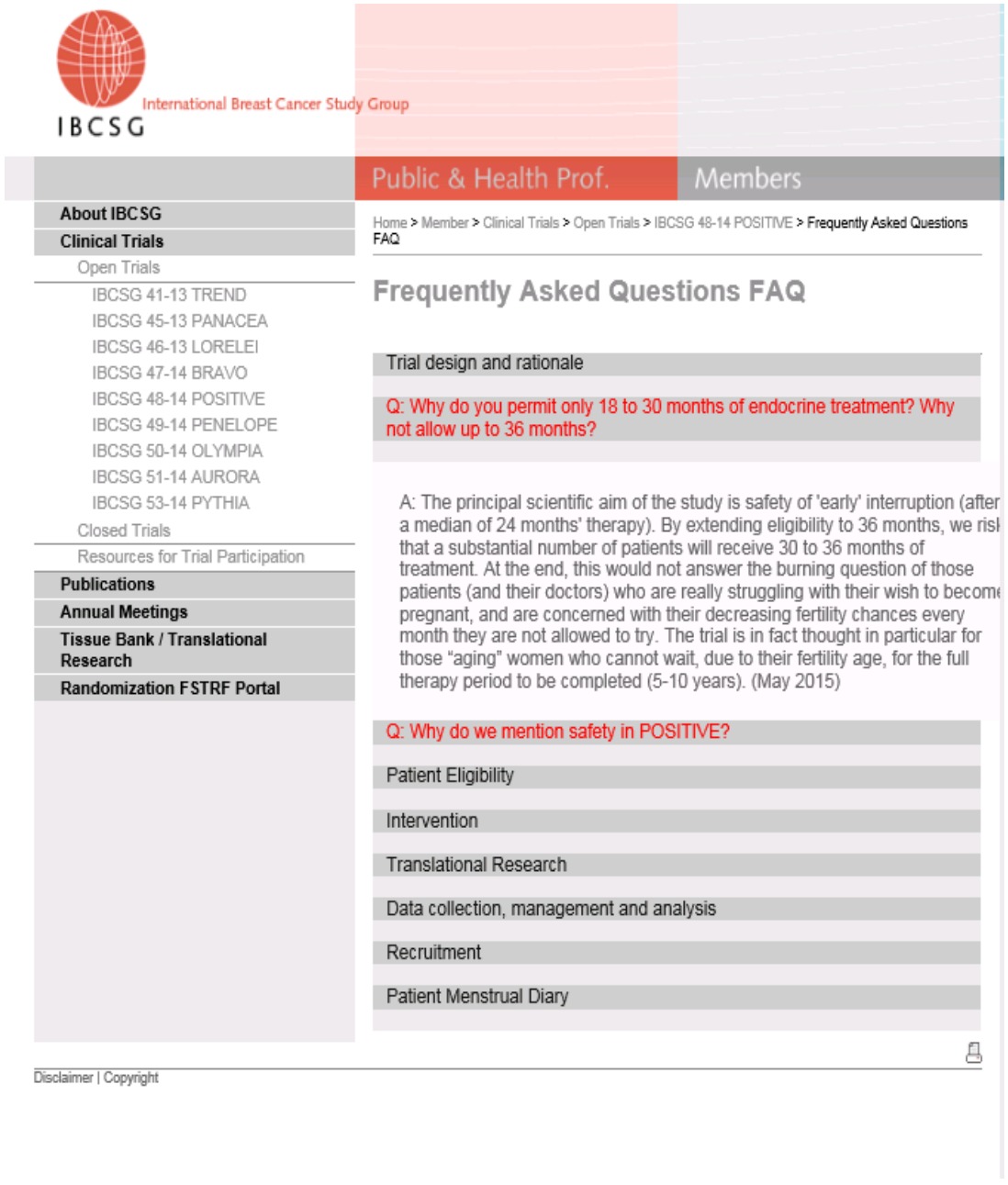
2. Was serum PRL done? (If high, repeat at month 12.)
   - ○ No
   - ◉ Yes
     - ◉ Normal
     - ○ High

3. Was serum TSH done? (If abnormal (low/high), repeat at month 12.)
   - ○ No
   - ◉ Yes
     - ○ Normal
     - ◉ Low
     - ○ High

RESOURCES

- IBCSG Website (www.ibcsg.org)
  - Protocols and Appendices
  - Frequently Asked Questions (FAQs)
  - Data Manager Manuals
  - Blood Sample Logistics
  - Reports (Safety, DSMC, Biostatistician)
  - Newsletters

- DataFax Resource Support Website
  - https://www.ibcsgdmc.org/ibcsg/df/



Please check the FAQs every few weeks for any new questions or important information

POSITIVE TRIAL

QUALITY ASSURANCE VS QUALITY CONTROL

QUALITY ASSURANCE AND QUALITY CONTROL WHAT'S THE DIFFERENCE

QUALITY CONTROL

Periodic operational checks within each functional department to verify that clinical data are generated, collected, handled, analyzed, and reported according to protocol, SOPs, and GCPs

MONITOR / DATA MANAGER TEAM

QUALITY ASSURANCE

The systematic and independent examination of all trial-related activities and documents. These audits determine whether the evaluated activities were appropriately conducted and that the data were generated, recorded, analyzed, and accurately reported according to protocol, standard operating procedures (SOPs), and good clinical practices (GCPs).

AUDIT TEAM

QUALITY CONTROL IN THE POSITIVE TRIAL

THIS IS A UNIQUE STUDY ALL OVER THE WORLD

YOU ARE THE PROTAGONIST OF THIS AMAZING STUDY

YOU ARE REQUESTED TO KEEP HIGH QUALITY OF WORK

Trial monitoring plan is minimal

IBCSG is not able to cover QC/QA costs all over the world – Low funds

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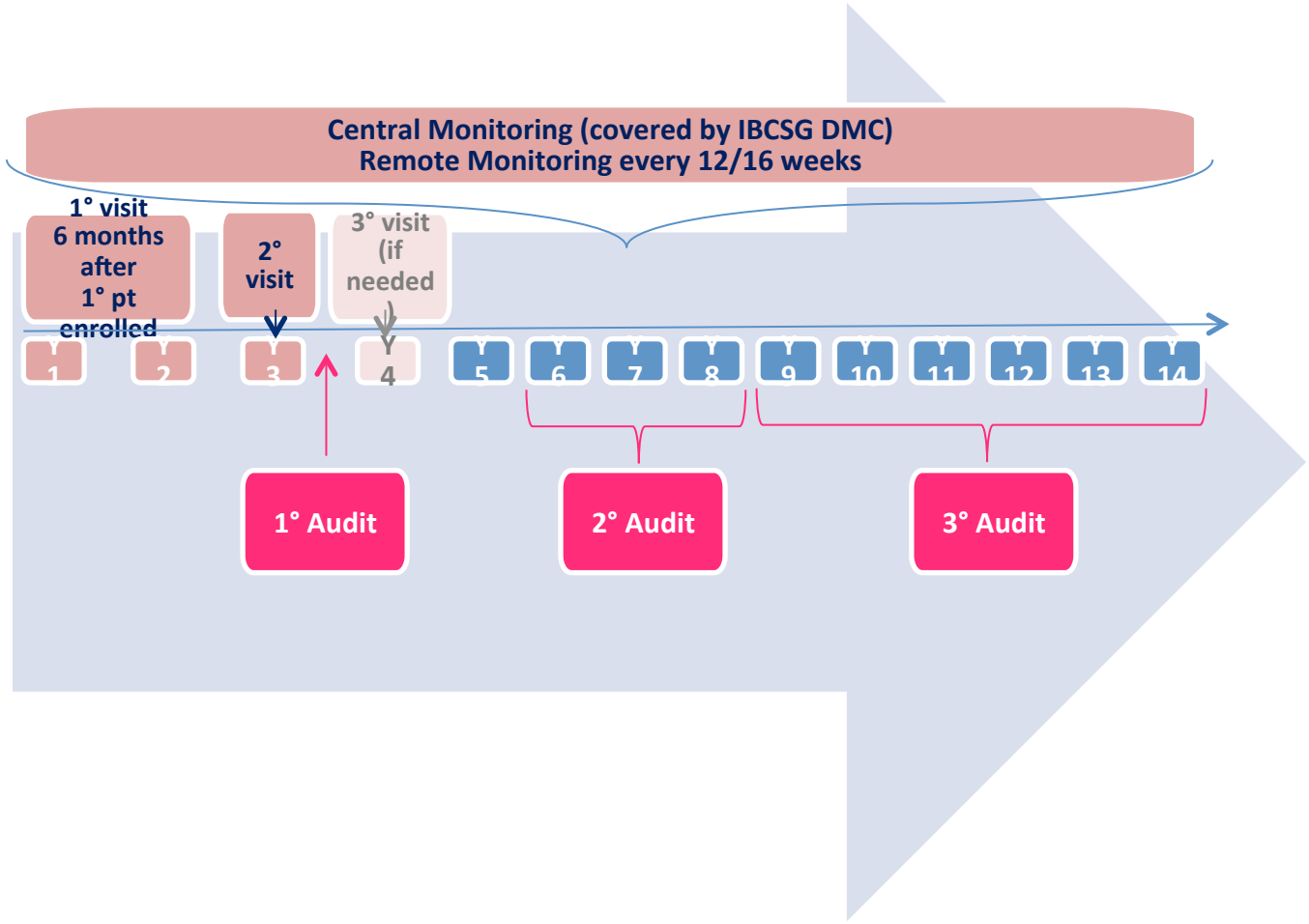
IBCSG 48-14 POSITIVE QC/QA TIMELINES



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HOW TO KEEP HIGH QUALITY

- Keeping Source Documents as updated as possible
- Keeping Idatafax as updated as possible
  - entering data and resolving queries in timely manner
- Supporting Monitor / Data manager during the routine
  - remote/on-site visits/central monitoring
- Resolving all pending issues after any remote/on-site visit
  - respecting the deadline agreed
- Being compliant with protocol and its procedures as much as possible
- Being available for any discussion, questions, feedback (PI and site staff)

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COMPLETENESS OF SOURCE DOCUMENTS

- INFORMED CONSENT PROCESS
  Patient has been informed about the protocol and its procedures
  Patient has had enough time to read and understand the consent
  Patient has received a copy of the consent

- SCREENING INFORMATION AND ITS PROCEDURES
  Patient wishes to become pregnant

- RANDOMIZATION INFORMATION AND ITS PROCEDURES
  Non hormonal contraceptive methods
  All inclusion/exclusion criteria verified. Patient is able to be enrolled

The monitor is on site and needs to confirm each tick box for the inclusion of the patient. What is the fastest and easiest way for all involved people?

Why do you think it is important, that the contraception method or the discussion about it is mentioned in the patient chart?

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NOT DOCUMENTED…NOT DONE

IF IT IS NOT DOCUMENTED, IT NEVER HAPPENED

IF IT IS NOT DOCUMENTED, IT DOESN'T EXIST

PROCEDURES: TRANSLATIONAL RESEARCH

CENTRAL EVALUATION: AMH, FSH, E2, Serum Progesterone, ctDNA

You are provided with an Initial kit which consists of: **Cryovials**, **Labels** (with appropiate blood draw time points and **cryoboxes**.

Step 1

Step 2

Step 3

All serum/plasma samples must be stored locally at -80°C (T deviation form in case T above -40°C)

TRANSLATIONAL RESEARCH IS A CRUCIAL ASPECT OF THIS STUDY AND ALL SAMPLES COLLECTED WILL BE CHECKED BY THE MONITOR AT EACH ON SITE-VISIT.

PROCEDURES: PATIENT DIARY

- Patient diary is provided to patient at time of registration
- Patient diary collects information about menses. Start point for completion is ET interruption (might be retrospectively if patient stopped up to one month prior to registration)
- The diary is also a reminder to the patient to have their obligatory blood draws during specified days in their menstrual cycle
- Patient diary needs to be signed both by Patient and Investigator at each visit

PATIENT DIARY IS A SOURCE DOCUMENT!

During an audit/inspection, patient diary of a certain patient is not available/not complete. What impact could it have?

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IBCSG 48-14/BIG 8-13 - POSITIVE STUDY
PATIENT MENSTRUAL DIARY

Patient ID:_____

Date of Enrollment in Study: __/____/_____

Date of ET Interruption: _____/_____/_____

You have decided to participate in this clinical research study and have temporarily interrupted the endocrine therapy you were receiving to be able to attempt pregnancy.

This diary will collect information on timing of your menstrual recovery after treatment interruption and on the pattern of your menses during your first two years of participation in the study. These data will provide additional information on factors potentially related to the ability to get pregnant.

Instructions: Use the Menstrual Flow Key to complete your menstrual diary for each menstrual cycle once you have enrolled in the study. Please use this diary as a reminder to schedule your blood draws during specific days of designated menstrual cycles. You should bring this diary with you to each appointment after you have signed it. Your physician will sign it, make a copy and store it in your chart.

Menstrual Flow Key:

H-Heavy: needed sanitary towels/ napkins as well as tampons. Large clots and/or 'flooding' (blood staining clothing or bed sheets)
M-Moderate: regular changes of towels or tampons. No social inconvenience.
L-Light: needing some protection to prevent staining of underwear, or very light loss staining underwear
N-No menses

Please use the Menstrual Flow Key to enter a letter that corresponds with each day of the month on the calendar provided.

You are advised to use effective non hormone-containing contraception or be abstinent while waiting three months after endocrine treatment interruption before attempting conception.

IBCSG 48-14/BIG 8-13 - POSITIVE STUDY
PATIENT MENSTRUAL DIARY

1st calendar month after stop of endocrine treatment: ..... (please write down name of month):

DAY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Menstrual Flow																															

Which contraception are you using?

Nothing ☐ Condom ☐ Non-hormonal Intrauterine Device ☐ Abstinence ☐ Diaphragm ☐ Other ☐, specify: _____

2nd calendar month after stop of endocrine treatment: ..... (please write down name of month):

DAY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Menstrual Flow																															

Which contraception are you using?

Nothing ☐ Condom ☐ Non-hormonal Intrauterine Device ☐ Abstinence ☐ Diaphragm ☐ Other ☐, specify: _____

Patient signature
Investigator signature

TAKE HOME MESSAGES

CRITICAL ASPECTS OF THIS TRIAL FROM THE MONITOR / DATA MANAGER PERSPECTIVE:

- COMPLETENESS OF SOURCE DOCUMENTS
- TRASLATIONAL RESEARCH
- PATIENT DIARY


Don't ask if it is going to be easy.
Ask if it's going to be worth it.
- Michael Josephson
START
whatwillmatter.com
Michael Josephson
charactercounts.org

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THANK YOU FOR THE ATTENTION

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