IMPAACT 2010
Action Taken in Response to Tsepamo Findings

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

IMPAACT 2010

Phase III Study of the Virologic Efficacy and Safety of Dolutegravir-Containing versus Efavirenz-Containing Antiretroviral Therapy Regimens in HIV-1-Infected Pregnant Women and Their Infants

VESTED

Virologic Efficacy and Safety of ART Combinations with TAF/TDF, EFV, and DTG

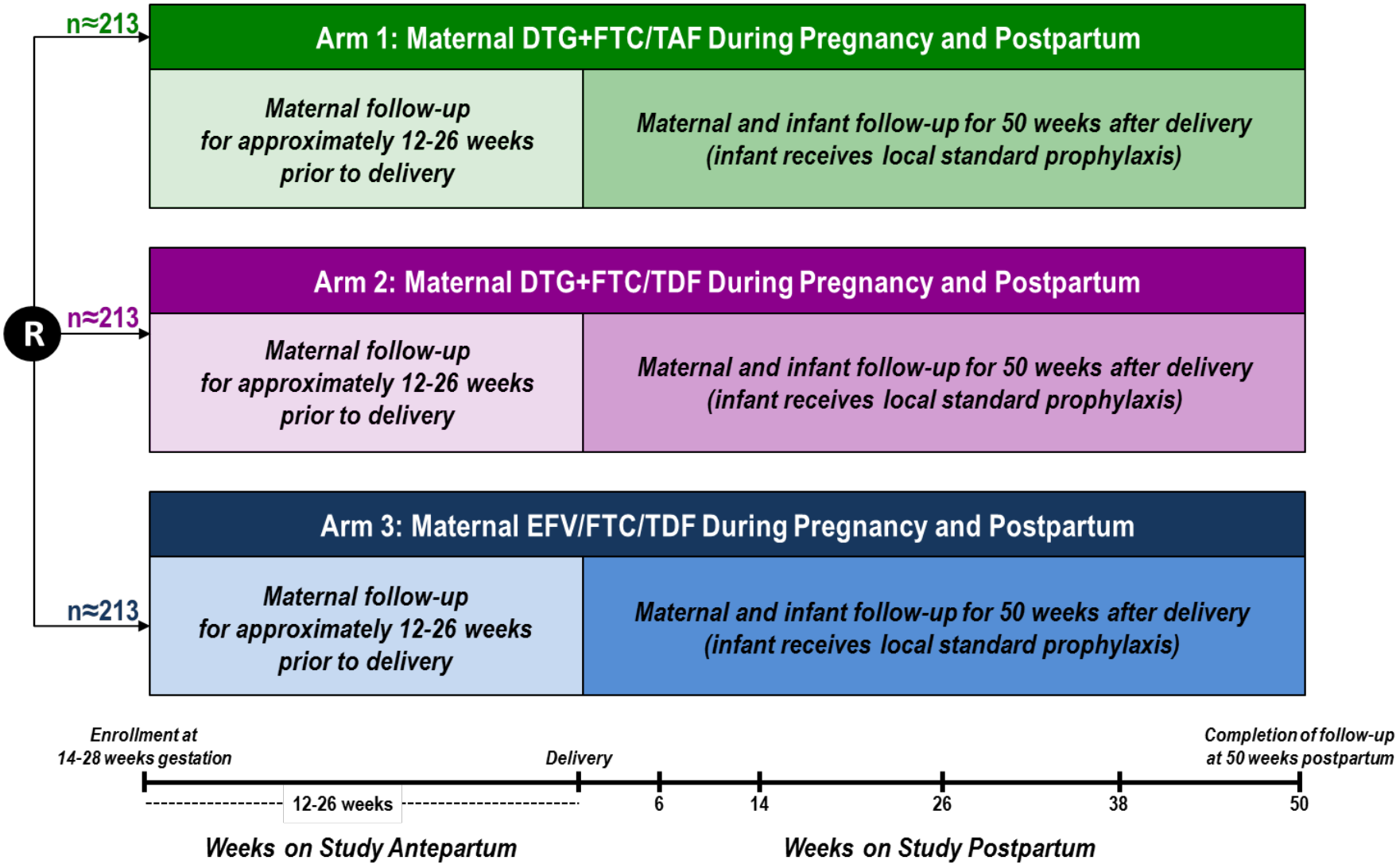
IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

VESTED

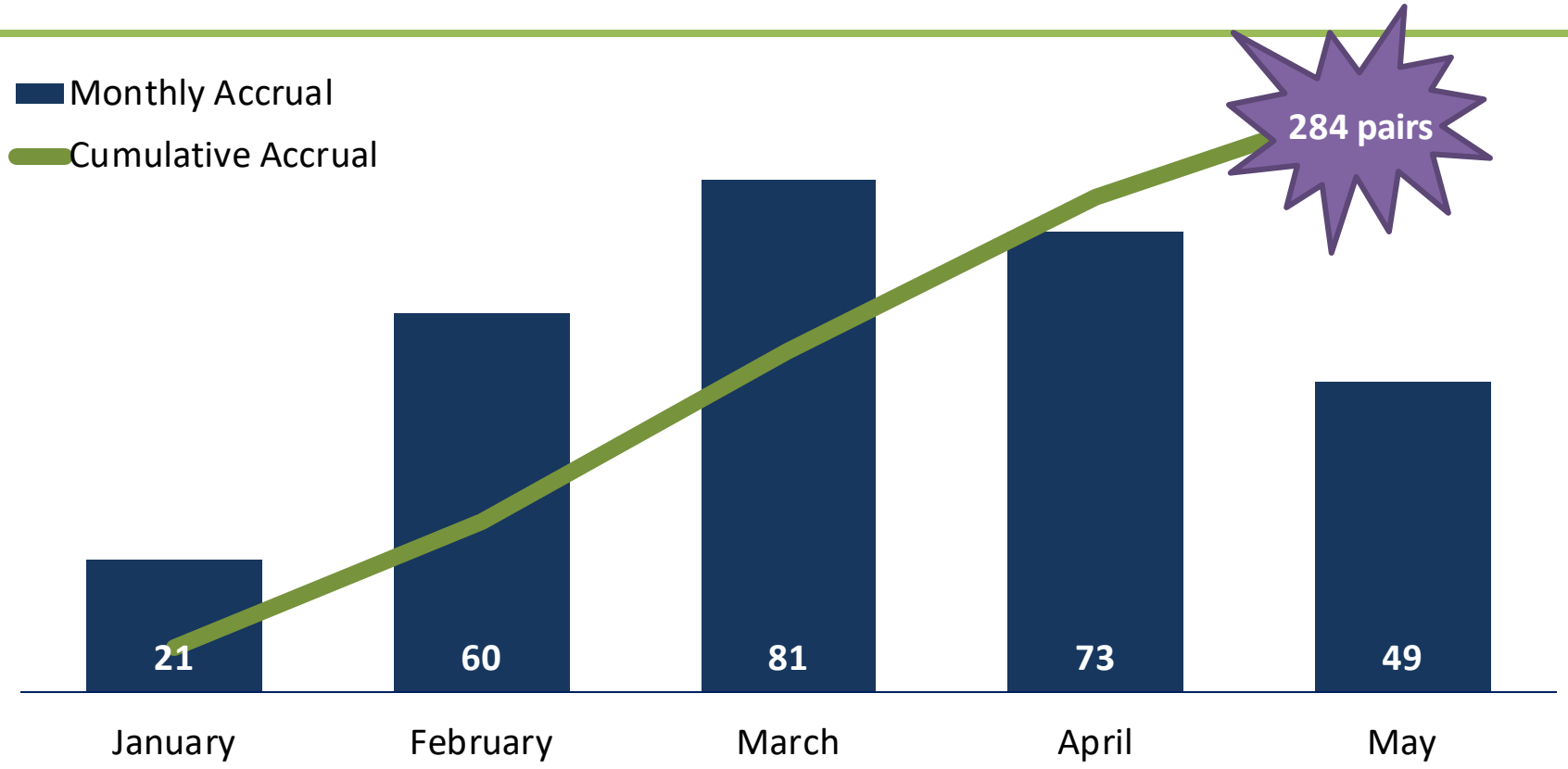
Design: Phase III, three-arm, randomized, open-label study

Population: HIV-1-infected pregnant women initiating antiretroviral therapy at **14-28 weeks gestation** and their infants

Sample Size: 639 mother-infant pairs (approximately 213 per arm)


n≈213
Arm 1: Maternal DTG+FTC/TAF During Pregnancy and Postpartum
Maternal follow-up for approximately 12-26 weeks prior to delivery
Maternal and infant follow-up for 50 weeks after delivery (infant receives local standard prophylaxis)
R
n≈213
Arm 2: Maternal DTG+FTC/TDF During Pregnancy and Postpartum
Maternal follow-up for approximately 12-26 weeks prior to delivery
Maternal and infant follow-up for 50 weeks after delivery (infant receives local standard prophylaxis)
n≈213
Arm 3: Maternal EFV/FTC/TDF During Pregnancy and Postpartum
Maternal follow-up for approximately 12-26 weeks prior to delivery
Maternal and infant follow-up for 50 weeks after delivery (infant receives local standard prophylaxis)
Enrollment at 14-28 weeks gestation
Delivery
Completion of follow-up at 50 weeks postpartum
12-26 weeks
6
14
26
38
50
Weeks on Study Antepartum
Weeks on Study Postpartum

Study Progress: Activation and Accrual

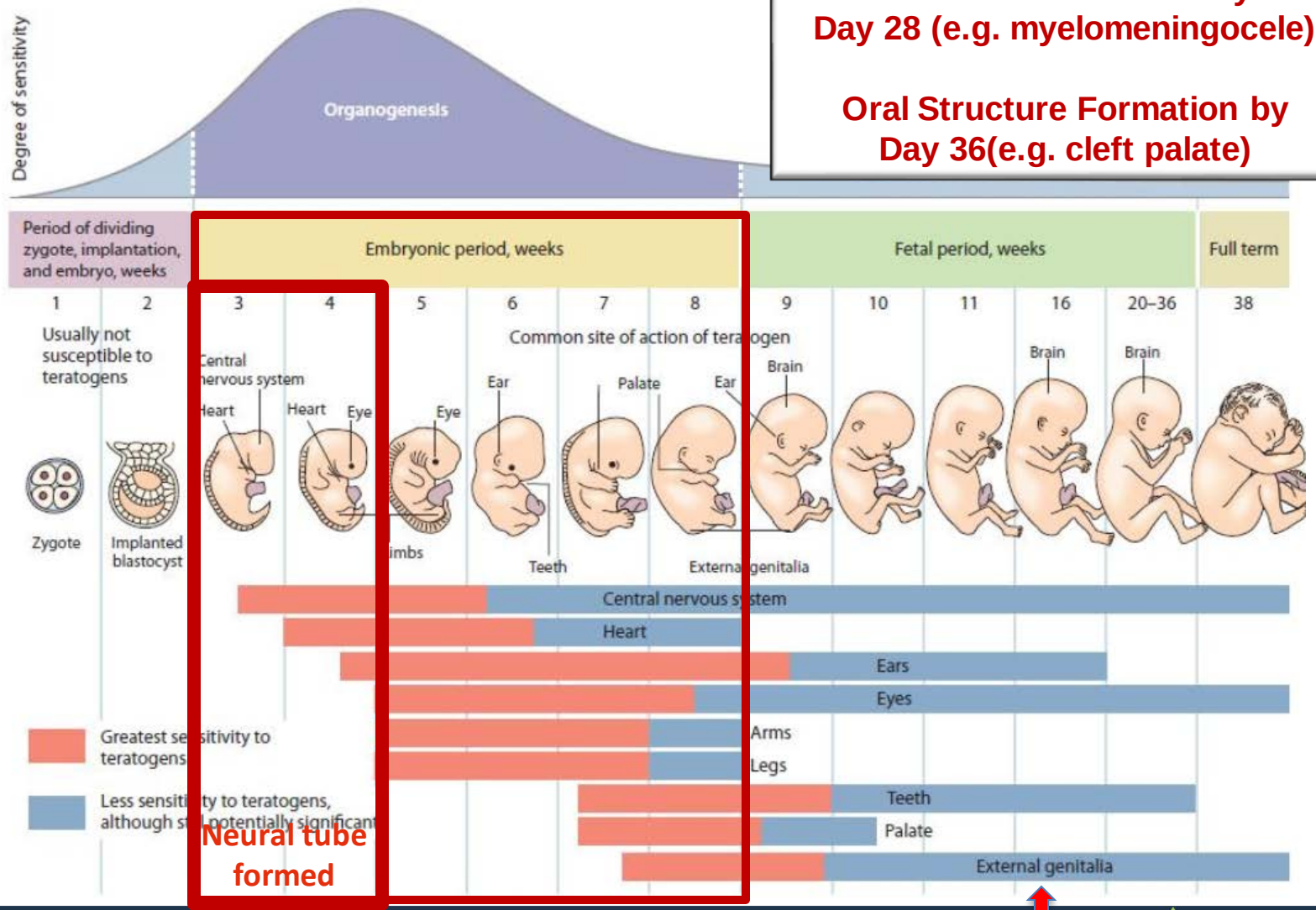


12702, Botswana 12701, Botswana 5118, Tanzania 31890, Zimbabwe 8052, South Africa 30303, Zimbabwe 30306, Zimbabwe 5051, US	30293, Uganda 4201, US 8051, South Africa 30300, South Africa	8950, South Africa 31798, Uganda	31874, Thailand 5072, Brazil 5073, Brazil	5115, Thailand 5097, Brazil

Timing of *In Utero* ARV Exposure and Fetal Risk

Examples:
Neural Tube Closure by Day 28 (e.g. myelomeningocele)

Oral Structure Formation by Day 36(e.g. cleft palate)



Adapted from slide from Lynne Mofenson

Weeks 3 to 8-12 Post-Fertilization: Embryogenesis/Active Organogenesis: most sensitive to teratogens

Safety Considerations, IMPAACT 2010

- Safety during the primary pregnancy:
  - Pregnant women entering IMPAACT 2010 start study ART at 14-28 weeks gestation
  - This is well after neural tube development
  - In the Tsepamo study
    - In 2,812 women starting DTG in pregnancy (similar to IMPAACT 2010), no babies born with NTDs
    - Rates of other adverse birth outcomes similar in women starting DTG- vs EFV- ART in pregnancy
  - There are no new data to suggest a safety concern when starting DTG in pregnancy

- Safety during subsequent pregnancies:
  - Tsepamo findings indicate potential concern for neural tube defects among babies of women taking DTG at the time of conception of a new pregnancy
  - In IMPAACT 2010, the period of concern is after the primary pregnancy, during the 50 weeks of postpartum follow-up, when a new pregnancy may be conceived

- Actions to protect participant safety:
  - Temporary enrollment pause, inform & counsel participants, postpartum contraception
  - Revise inform consent forms to include new findings from the Tsepamo study
  - Revise protocol to only enroll women not planning new pregnancy in year after delivery
  - Revise protocol to require reliable contraception postpartum and to switch off DTG to different ARV, if do not want to/cannot use contraception

Rationale for Continuing IMPAACT 2010

- The signal for NTD with pre-conception DTG arose from a relatively small number of pregnancies (426) in one location/study
  - Significant effort is underway to gather more data to determine whether signal persists (is confirmed) or whether was due to chance
  - If this signal is not confirmed, IMPAACT 2010 data particularly important
- Study is being modified to ensure use of effective contraception in women in the postpartum period, and enrollment of women who do not wish to become pregnant during the study
- No new safety concern regarding **starting** DTG in pregnancy
- DTG remains superior to EFV with regard to efficacy/tolerability in adults and has much higher resistance barrier – preferred ARV
  - Important to offer optimal ART to all PLWH when possible, including women
  - DTG is associated with faster viral load decline: particularly important for pregnant women starting ARV in late 2nd or in 3rd trimesters
- IMPAACT 2010 is also providing the only substantial safety data related to tenofovir alafenamide (TAF) vs. TDF in pregnancy
  - TAF shown to be safer and cheaper to make than TDF (and as effective)

Action to Date

- **18 May 2018**
  - Information about NTDs with DTG from conception first made public.
  - Accrual into IMPAACT 2010 was temporarily paused (5pm EDT).
- **21 and 22 May 2018**
  - Site investigators were advised by the Protocol Team to inform enrolled participants of the potential increased risk of NTDs, with priority placed on urgently informing participants who have delivered and are receiving DTG postpartum.
  - Talking points were provided for these initial discussions, emphasizing the need for contraception to avoid pregnancy and advising a switch off DTG postpartum for participants who wish to become pregnant or who do not wish to use contraception while taking DTG postpartum.
  - The Protocol Team also recommended that sites inform IRBs/ECs, applicable regulatory entities, and other stakeholders of the initiation of this activity.

Action to Date

- **24 and 25 May 2018**
  - ViiV Healthcare Safety Advisory letter to investigators and DAIDS guidance to protocol team received
- **29 May 2018**
  - E-survey was distributed to sites requesting information on capacity to provide effective contraceptive methods and to perform fetal ultrasound scans for purposes of identifying structural abnormalities
- **31 May 2018**
  - Team responded to DAIDS request (within 3 business days) to submit a draft Dear Investigator Letter, Dear Participant Letter, and protocol Letter of Amendment
- **June 7 2018**
  - Notified DSMB of new information re: NTDs, and action taken / planned

Action to Date

- **31 May 2018**
  - Team submitted draft Dear Investigator Letter, Dear Participant Letter, and protocol Letter of Amendment (LoA) for DAIDS review
- **11 June 2018**
  - DAIDS regulatory review comments on LoA received
- **14 June 2018**
  - Final DAIDS comments on letters received
- **15 June 2018**
  - Dear Investigator and Dear Participant Letters distributed to team and sites (LoA to follow pending discussion at the IMPAACT Annual Meeting)

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
					May 18 Results; Accrual paused	19
20	21 Team+Site Investigator Call	22 Talking Points & Materials to Sites	23	24 ViiV Safety Advisory Letter	25 DAIDS Directives to Team	26
27	28 (US Holiday)	29 Contraceptive Access Survey to Sites	30	31 Letters and LoA submitted to DAIDS	June 1	2
3	4	5	6	7	8	9
10	11 Reg review comments on LoA received	12	13	14 Final DAIDS comments on letters	15 Letters to Sites	16
17	18	19				

Action Specified in Letters and LoA

- New study eligibility criterion: willingness to use effective contraception, and no desire to become pregnant again during postpartum study period
- Routine provision of contraception counseling at all scheduled maternal study visits
  - *The benefits of child spacing (and maternal folate supplementation) for maternal and child health should be emphasized to all mothers*
  - *The importance of avoiding pregnancy while on DTG should be further emphasized to mothers taking DTG postpartum*
  - *All mothers should be counseled to use condoms for dual protection against pregnancy and to avoid transmission of HIV and other sexually transmitted infections*

Action Specified in Letters and LoA

- Routine provision of, or active referral to, contraceptive services at all scheduled maternal postpartum study visits
  - *An effective method of contraception should be initiated as soon as clinically appropriate after delivery*
  - *Effective methods include any of the following, in combination with condoms:*
    - ❖ Contraceptive intrauterine device or system
    - ❖ Subdermal contraceptive implant
    - ❖ Percutaneous contraceptive patch
    - ❖ Contraceptive vaginal ring
    - ❖ Progestogen injections
    - ❖ Progestogen only oral contraceptive pills
    - ❖ Combined estrogen and progestogen oral contraceptive pills

Action Specified in Letters and LoA

- Routine reminders to inform study staff of any desire to become pregnant or any suspicion of pregnancy at all scheduled maternal postpartum visits.
- Routine pregnancy testing at all scheduled maternal postpartum visits.
- Discontinuation of DTG (switched to another antiretroviral agent) for any mother who expresses a desire to become pregnant or is otherwise unwilling or unable to use effective contraception.

Action Specified in Letters and LoA

- Offer participants who become pregnant again a referral for fetal anatomical ultrasound between 14-22 weeks gestation
- To permit eventual exploratory evaluation of potential mechanisms of NTDs:
  - Stored samples for RBC folate level (mothers: at entry, 12 weeks, and delivery; babies at birth)
  - Maternal HbA1C testing (+/- maternal and infant glucose)

Other Ongoing and Expected Action

- Follow-up of 284 previously enrolled mother-infant pairs is continuing
- Sites that initiated the study first, under Version 1.0, are transitioning to Version 2.0 as approvals are received
  - Requires re-consenting for Version 2.0 ***in addition to*** administering the Dear Participant Letter (which is discussed and signed similar to an informed consent form)
- Following approval of both protocol Version 2.0 and the forthcoming LoA, participant accrual will be resumed on a site-by-site basis, with re-consenting required for the LoA

What are your questions?