“Real-Time” Pharmacologically-based Adherence Testing: Views from the Laboratory

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Context

- Undetected poor adherence, not drug effect, led to PrEP efficacy failure in several RCTs
- Subjective methods of adherence assessment were misleading in all of these RCTs
- Pharmacologic data provides objective, semi-quantitative evidence of medication adherence
- Recommended implementation of ongoing "real-time" pharmacologically-guided adherence assessment in future RCTs

MTN
microbicide trials network

Implementation: MTN-017 & MTN-020

- MTN-017
- Phase 2 *open label*
- Safety & acceptability
- Rectal 1% TFV gel
- 8 Sites
- PK sampling mid & end period visit (3, 4, 6, 7, 9, 10)
- Adherence testing
  - Bi-weekly shipments
  - <60
  - Individual testing
  - *Individual* feedback *next visit*

- MTN-020 (ASPIRE)
- Phase 3 RCT *blinded*
- Efficacy
- Dapivirine 25 mg vaginal ring
- 14 Sites
- PK sampling quarterly visits

- Adherence testing
  - Monthly Shipments
  - 500 samples (↑ 750 Spring 2015)
  - Individual testing
  - *Site level* feedback

MTN-017 "Real-time-enough" Testing?

Study Site	Total # Shipments	Average Turn Around Time*
Bangkok	14	10
Boston	13	8
Capetown	19	9
Chiang Mai	25	9
Lima	22	8
Pittsburgh	31	8
San Francisco	30	8
San Juan	20	8

*From ship date

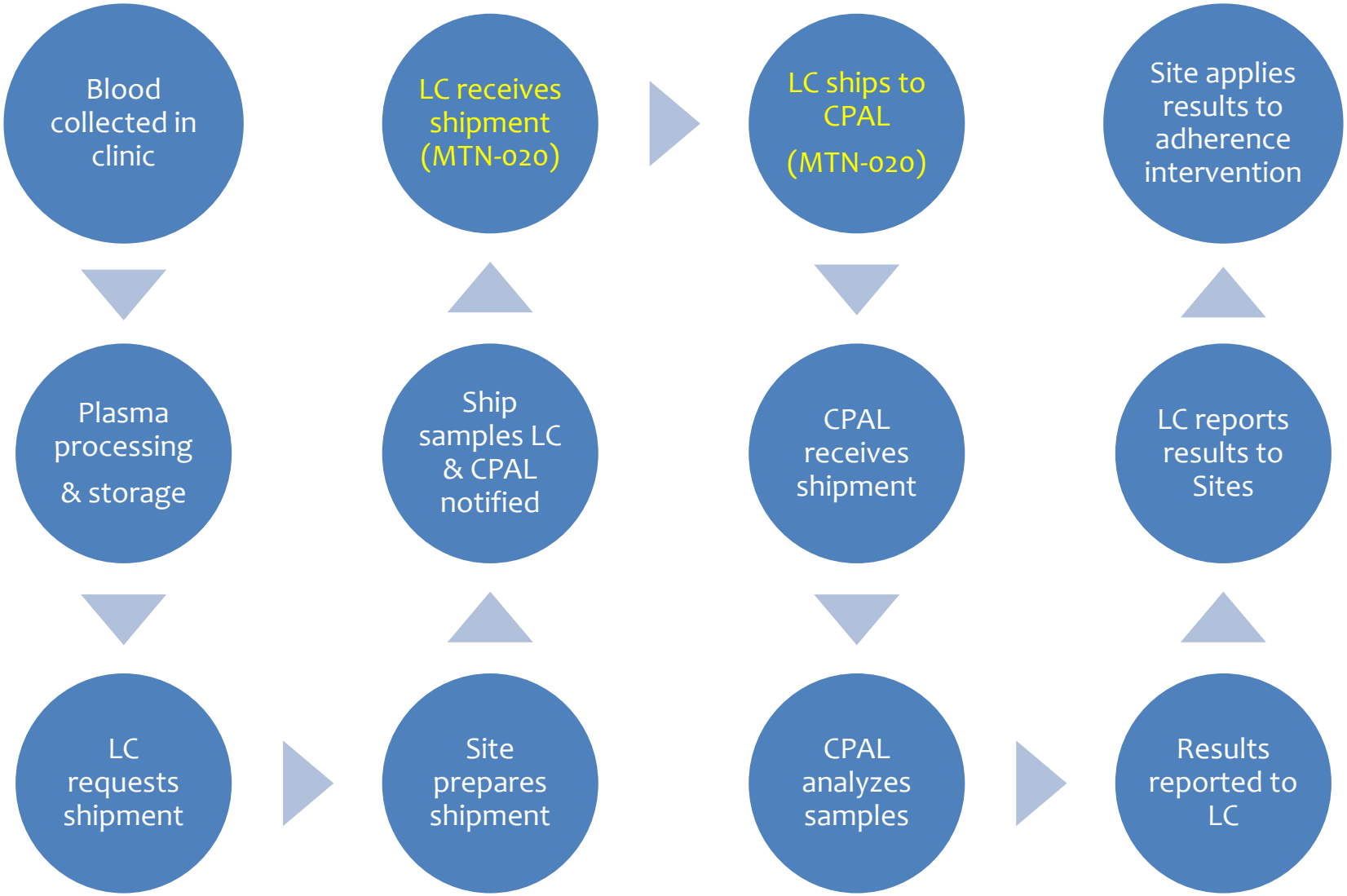
MTN-020 "Real-time-enough" Testing?

- Request samples from sites ~monthly
- Receive at MTN LC Pittsburgh
- Ship to CPAL when 1,000 amassed (500 shipped)
- Report from CPAL within 2 weeks

Study Site	Sample Retrieval Time*	Comments
CAPRISA	12	
MRC	13	
BARC (WRHI+Capetown)	16	Ship CPT to JNB before to US
Lilongwe+Blantyre	17	Ship between sites before to US
MU-JHU	20	
UZ-UCSF	22	Need permit for each sample list

*Days between shipping request and samples' arrival in MTN LC (Pittsburgh)

“Real-Time” Testing Process



Clinical Pharmacology Analytical Laboratory (CPAL)

- Schedule
  - Bi-weekly (MTN-017) & monthly (MTN-020) specimen receipt, inventory, storage, processing
  - > 2 weeks per month sample analysis, QA, reporting
  - ~7-8,000 reported results annually
- Personnel
  - 1 inventory/storage/supply technician (~1 wk/mo)
  - 2 junior technicians (most of effort 2 wks/mo)
  - 1 faculty CPAL Director (scheduling, supervision, QA, 25%)
- Equipment
  - Sample prep (extraction) equipment
  - Mass spectrometer (API 4000)
- Overall CPAL impact
  - 2.5 of 5.5 personnel FTE (45%)
  - 7,500 of 19,000 assays reported (42%)

Mark Marzinke, PhD
CPAL Director

CPAL Reflections

- *We make this mission critical program work*
- Coordination between LC, sites, CPAL amazing
- Constant burden, disproportionate effort
- Samples direct from sites rarely works well; LC as central receiving/distribution better
- By-passing LDMS (MTN-017) risky; needs improvements to assure quality
- Bi-weekly low volumes (MTN-017) inefficient

Recommendations

- Evaluate relative role of PK, EMS, SMS impact
- Continue *selectively, e.g.,* pivotal clinical studies
  - "If everything is real-time, nothing is"
- Site level intervention can use partial sampling
- Qualitative PK methods
  - faster, but usually less sensitive, less appropriate for topical
- Match sampling visit interval to PK matrix
  - Trades off processing time, lab capacity, does time allow?
  - Matrix selection requires more development, esp. ring assay
- Site of dosing monitoring
  - Cuts feedback delay, all ppts (not just active), lower cost than PK, enables adherence reinforcement, incl. $$ transfers
- Provide feedback to CPAL as motivation

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