Experiences with co-enrollments in CAPRISA 004 & HPTN 035:
Lessons for Future Trials

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Outline

- Discovery of ineligible enrollments
- Audit findings
- Addressing the problem
- Mistakes made in the process
- Reasons for co-enrollment
- Impact on CAP004 trial
- Conclusion
Discovery of co-enrollments & implementation of measures to prevent further co-enrollments

First suspicion: Nurse at eThekwini clinic identified MRC nurse’s handwriting on patient’s Family Planning card

Cross-checking procedures initiated with MRC to check ID numbers of all new women being screened at eThekwini

CAPRISA 004 participant returned HPTN 035 gel applicators to the pharmacy at eThekwini → co-enrollment confirmed by MRC. Audit conducted to establish full extent of problem

Enrollments at the eThekwini site put on hold & terminations initiated.

Cross-referencing of SA ID numbers of all CAPRISA 004 and MRC study participants.
Audit Findings

135 co-enrolled in CAPRISA & MRC microbicide studies:

- 96 HPTN 035 participants enrolled in CAPRISA 004
- 35 participants in other MRC studies enrolled in CAPRISA 004
- 4 CAPRISA 004 participants enrolled in MRC studies
Communication of Findings

- Set up active lines of communication with MRC
- Ethics Committees
- South African Medicines Control Council
- Research Community & Public - CAPRISA Newsletter
- Urgent CAP004 PSRT review of safety
- CAP004 DSMB met to review the safety monitoring data and...

“found no safety concerns in both groups of ineligible participants – the co-enrolled participants as well as in the ineligible participants who were not co-enrolled.”
Addressing the problem

On-line ID number checking

- Radio-link between UKZN & MRC
- Existing MRC database converted to shared database system with partitions
- Upgrade of existing MRC software
- Scanners to read ID numbers – reduce transcription error problem
Addressing the problem

- **Ethics approval obtained**
  - Condonation for ID checking since 14 Feb 2008
  - Approval for ongoing checking
  - Approval of ID checking system (BREC imposed rules)
  - More info needed for opinion on fingerprint checking

- **SOPs and Staff training**
  - New SOPs for checking of ID numbers
  - Designated staff on each study: entering & checking ID numbers
  - ID checking now in specific job descriptions
Ongoing detailed investigation: Root cause analysis

- Root cause analysis comprised:
  - Written accounts from each person involved
  - Copies of all e-mails
  - Interviews with staff
  - Focus group discussions with groups of staff

- Internal report: Basis for remedial actions, new procedures, messaging & staff training

- Questionnaires administered to all participants to understand why they co-enrolled

- Detailed analysis of ineligible participants ongoing
Mistakes made by CAP004 PIs

- Failure to anticipate the possibility of co-enrollment.
  - No systems were in place to identify and address the issue of co-enrolled participants.

- Incorrectly assumed the following 3 barriers would be sufficient to prevent co-enrollments:
  - Closest MRC site is over 25km away from the eThekwini site
  - Recruitment mainly from Prince Cyril Zulu STD clinic
  - Depended on self-report to exclude co-enrollment

- Should not have allowed community recruitment
Reasons for co-enrollment

- R150 financial incentive
- Access to quality health care
- Altruism: want to contribute to AIDS research
- Want to increase chances of getting active gel
- Peer influence (waiting rooms: source of info)
- Want to continue gel because it improves sex
- Impunity: did not think they would get caught
Impact on CAP004 trial

- Impact on cost (wasted enrollments & new systems)
- Study team morale severely affected
- New stringent accrual procedures – slowing accrual
- Impact on trial integrity
  - Lost 47 person-years at one site
  - Fortunately ID numbers obtained prior to randomization – so exclusion based on ID numbers should not introduce bias – Sensitivity analysis
- Impact on timelines: trial to be completed 2 months after the anticipated completion date by:
  - increasing sample size by 270
  - accruing over 5 additional months
Conclusion

- No single simple reason for root cause of co-enrollments.
- New measures to avoid future co-enrollments using ID numbers is working well
- Ethically acceptable ID checking
- Assessing two different fingerprint systems
- Important: Be aware that it can happen – even same participant enrolling twice