



CAPRISA

CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA



CAPRISA IS A UNAIDS
COLLABORATING CENTRE
FOR HIV PREVENTION RESEARCH

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

Salim S. Abdool Karim

Director: CAPRISA

Pro Vice-Chancellor (Research): University of KwaZulu-Natal

Professor in Clinical Epidemiology, Columbia University

Adjunct Professor in Medicine, Cornell University

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

February 2008						
SUN	MON	TUE	WED	THU	FRI	SAT
					1	2
FEBRUARY						
	3	4	5	6	7	8
<p>First suspicion: Nurse at eThekwini clinic identified MRC nurse's handwriting on patient's Family Planning card</p>						
	10	11	12	13	14	15
	16	17	18	19	20	21
	22	23	24	25	26	27
	28	29	30			

March 2008						
SUN	MON	TUE	WED	THU	FRI	SAT
						1
MARCH						
	2	3	4	5	6	7
	8	9	10	11	12	13
	14	15	16	17	18	19
<p>Cross-checking procedures initiated with MRC to check ID numbers of all new women being screened at eThekwini</p>						
	21	22	23	24	25	26
	27	28	29	30	31	

April 2008						
SUN	MON	TUE	WED	THU	FRI	SAT
		1	2	3	4	5
APRIL						
	6	7	8	9	10	11
<p>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</p>						
	13	14	15	16	17	18
	19	20	21	22	23	24
	25	26	27	28	29	30

May 2008						
SUN	MON	TUE	WED	THU	FRI	SAT
MAY						
	1	2	3	4	5	6
<p>Enrollments at the eThekwini site put on hold & terminations initiated.</p>						
	8	9	10	11	12	13
<p>Cross-referencing of SA ID numbers of all CAPRISA 004 and MRC study participants.</p>						
	15	16	17	18	19	20
	21	22	23	24	25	26
	27	28	29	30	31	

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 eThekweni 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**