

The logo for ASPIRE features the word "ASPIRE" in a bold, purple, sans-serif font. A green ring is positioned around the letter "A". A thin green horizontal line is located below the word "ASPIRE".

A Study to Prevent Infection
with a Ring for Extended Use

Jared Baeten MD, PhD

Thesla Palanee, PhD

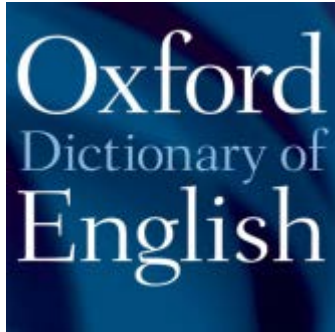
Implementation Update

ASPIRE Protocol Team Meeting

February 2014



What does ASPIRE mean?



aspire(as·pire)

Pronunciation: /ə'spɪ(ə)r/

verb

[*no object*]

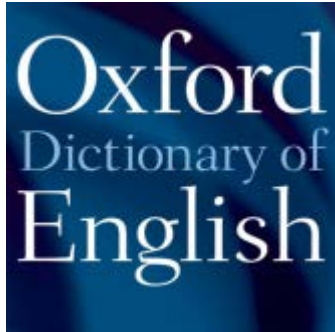
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*we never thought that we might **aspire to** those heights*

[*with infinitive*] :

*other people will **aspire to** be like you*

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ASPIRE

\ə-'spɪ(-ə)r\

noun:

1. A Phase III study that seeks to determine whether a woman's use of a vaginal ring containing dapivirine is a safe and effective method for protecting against HIV infection.
2. **A Study to Prevent Infection with a Ring for Extended Use**

verb:

1. **To seek to end the HIV epidemic** < *We **aspire to** prevent HIV*



Outline

- Meeting overview

- Past

- Present

- Future





Meeting overview

- A great day:
 - MORNING: focus on ASPIRE, Ring Study, CAT and Lab updates
 - AFTERNOON: Qualitative work, BRWG update and how to prep for Regulatory inspections, 015 and 016
 - THROUGHOUT: strong coffee and remembering our Big 5 metrics, working together as a team



Past

MTN-020 / ASPIRE

- **A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Phase III Safety and Effectiveness Trial of a Vaginal Matrix Ring Containing Dapivirine for the Prevention of HIV-1 Infection in Women**



The Big Five

Accrual

**Data Quality
and Timeliness**

Retention



**Clinical and
Laboratory
Safety**

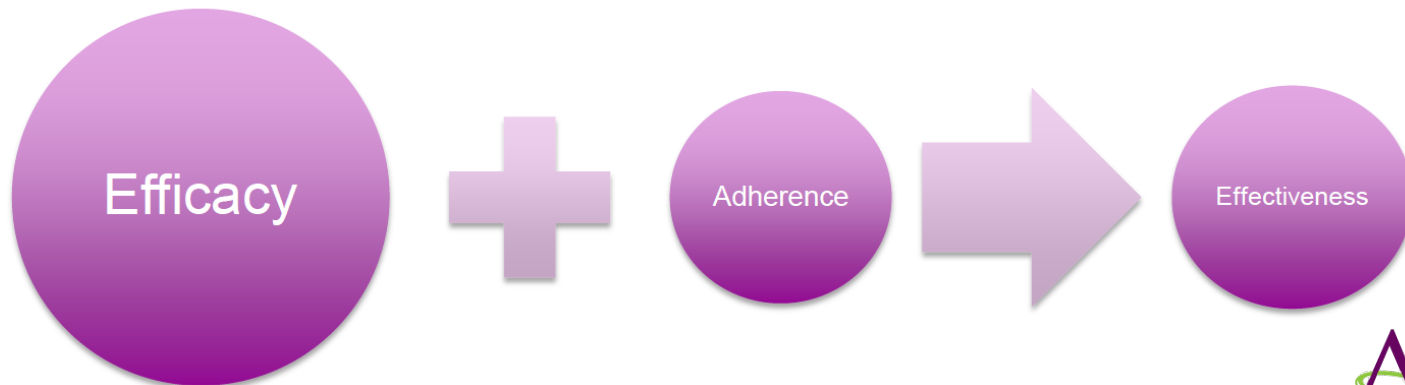
ASPIRE
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Adherence

ASPIRE calendar

- January 2011 and ongoing
 - Multilevel consultations on the science and implementation, leading to protocol version 1.0 in September 2011
- August 2012 - present
 - Start and go! Enrollments, follow-up, highest-quality execution of all protocol aspects
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 - **DSMB review**

Efficacy and effectiveness



March 2013: learning from PrEP trials

	HIV protection for FTC/TDF versus placebo	% of blood samples with tenofovir detected
Partners PrEP	75%	81%
TDF2	62%	79%
iPrEx	44%	51%
FEM-PrEP	No HIV protection	~30%
VOICE	No HIV protection	~30%

No adherence = no HIV protection



Adherence is Everything

Jared Baeten MD PhD
Thesla Palanee PhD

ASPIRE Adherence Meeting
Durban, South Africa
14 March 2013

ASPIRE
A Study to Prevent Infection
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Adherence Action!

□ Products don't work if they aren't used

□ Since March 2013:

Recognition of priority : scale-up across sites

Participant and staff engagement activities

IoR and SCs involved with difficult participants counselling

Fun waiting room discussions and social events

HIV ribbon and ring activities

Male partner engagement efforts

Visual inspection of the rings

PK data reviewed, shared, and acted upon

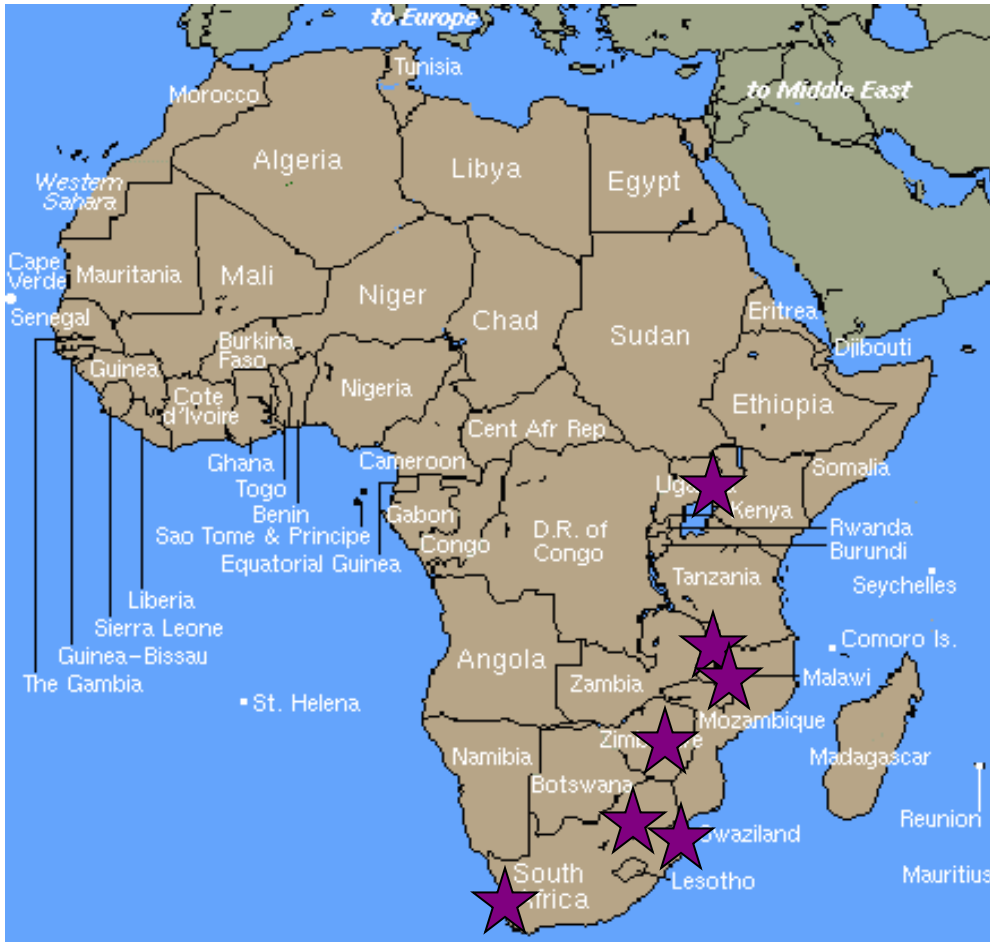
Learning from qualitative component of ASPIRE

Collection of used rings



Present

15 Sites across 4 countries



Blantyre
Lilongwe
Malawi

Cape Town
Durban (7 sites)
Johannesburg
South Africa

Kampala
Uganda

Harare/Chitungwiza (3 sites)
Zimbabwe

Accrual (19 Feb 2014)

Site	First enr	# enr	scr:enr ratio
MA – Blantyre	13 JUN 13	85	1.5
MA – Lilongwe	17 JUN 13	84	1.4
SA – Cape Town	19 SEP 2012	150	1.3
SA – CAPRISA eThekwini	10 OCT2012	176	3.1
SA – MRC/Botha's Hill	10 SEP 2012	147	2.3
SA – MRC/Chatsworth	11 SEP 2012	125	2.8
SA – MRC/Isipingo	19 SEP 2012	117	2.7
SA – MRC/Tongaat	17 SEP 2012	103	3.3
SA – MRC/Verulam	13 SEP 2012	118	2.4
SA – MRC/Umkomaas	14 SEP 2012	87	2.5
SA – WHRI/Hillbrow	30 OCT 2012	167	1.8
UG – Kampala	21 AUG 2012	243	1.5
ZI – Seke South	01 NOV 12	193	1.9
ZI – Spilhaus	30 OCT 12	195	1.7
ZI– Zengeza	13 NOV 12	179	1.8
TOTAL		2169 (!!!)	2.1

Enrolments

- 2169 – on schedule to achieve current targets in ~May 2014!



Screen outs

- As of 19 February 2014:
 - 4503 screened, 2168 enrolled (2.1 ratio)
 - 261 did not complete screening
 - 28 declined enrollment
 - 2046 ineligible
 - 777 (38%) HIV+
 - 172 (8%) pregnant; 27 (1%) breastfeeding
 - 408 (17.5 %) clinical/laboratory exclusion
 - 572 (28%)“other” including investigator decision

Who is enrolling?

- Mean age: 27.3 years, Median: 26 years
 - 39% <25 years, 14% ≥35 years
- Unmarried: MA (19%), SA (92%), UG (34%), ZI (16%)
- Secondary schooling complete : MA (11%), SA (45%), Zim (5%), and Uganda (50%).
- 100% had a primary partner in past 3 months
 - 18% had ≥1 other partner in past 3 months

Retention : As at 12 Feb 14

- 2001/2044 Month 1 visits (98%)
- 1911/1982 Month 2 visits (96%)
- 1801/1877 Month 3 visits (96%)
- 1713/1810 Month 4 visits (95%)
- 1619/1720 Month 5 visits (94%)
- 1527/1643 Month 6 visits (93%)
- 1467/1568 Month 7 visits (94%)
- 1347/11485 Month 8 visits (93%)
- 1278/1375 Month 9 visits (93%)
- 1182/11288 Month 10 visits (92%)
- 1101/1204 Month 11 visits (91%)
- 981/1083 Month 12 visits (92%)
- 812/912 Month 13 visits (89%)
- 681/779 Month 14 visits (87%)
- 587/669 Month 15 visits (88%)
- 374/420 Month 16 visits (89%)
- 150/172 Month 17 visits (87%)
- 35/37 Month 18 visits (95%)

**FEW MISSED VISITS AND
RINGS ARE OFTEN
DISPENSED AHEAD OF
PLANNED MISSED
VISITS!**

RETENTION SUMMARY:

OVERALL = 93.3%
EXCLUDING TERMS = 96.6%
LAST 3 MONTHS = 96.8%

Adherence Measurements and Monitoring

- We have learned much (and reacted to much) about non-use, non-interest?
 - Who returns without rings in place? Rings coming out?
 - IoR discretion to terminate ppts who are non-adherent to study visits or product
 - Qualitative interviews, staff observations
 - Blood and swab samples
 - Off-site visits to deliver rings
 - Ring drug level assessments

Data Quality and Timeliness

January 2014

Previous Month: January 2014

Site	Total Records	Total QCs	QC Rate Per 100 Records	% CRF Pages Received Within 7 Days	Mean Days to Fax in AE
Spilhaus/Zimbabwe	2135	25	1.2	98%	4.8
Seke South/Zimbabwe	2024	21	1.0	99%	4.4
Blantyre/Malawi	764	43	5.6	100%	24.7
Lilongwe/Malawi	786	13	1.7	30%	19.6
MRC - Chatsworth	966	29	3.0	97%	4.0
MRC - Botha's Hill	1247	67	5.4	95%	9.8
MRC - Umkomaas	685	35	5.1	94%	1.5
MU-JHU/Kampala, Uganda	2368	73	3.1	98%	4.7
Zengeza/Zimbabwe	1688	18	1.1	99%	2.7
MRC - Isipingo	1161	32	2.8	99%	1.2
MRC - Tongaat	1044	32	3.1	99%	6.4
MRC - Verulam	1137	20	1.8	100%	0.3
CAPRISA eThekwini	1794	97	5.4	98%	3.7
WRHI/Johannesburg	1583	69	4.4	96%	3.9
Emavundleni/Cape Town	1496	51	3.4	100%	17.5
TOTAL	20878	625	3.0	96%	7.7

Use of iDatafax

Safety

- Safety is the co-primary endpoint of the study
 - Evaluating whether the product is safe is just as important as whether the product is effective for HIV prevention
 - Regulatory authorities will scrutinize safety data and careful attention to safety documentation is critical

Contraceptive Action Team

- Meeting in Johannesburg : Feb 2014
- Incredibly motivated and innovative approaches to broaden contraceptive mix, counsel on highly-effective and safe methods, and provide methods on site
- Coming soon : Implants in SA
- Real change

Laboratory

- Laboratory results and archived samples are central to this study
 - Sample shipments
 - Ring Shipments
-
- THANK YOU FOR ALL THE HARD WORK

Team communications

- Monthly Protocol team calls
 - Tremendously valuable, site-driven, sharing experiences
- IoR calls regards the PK data
- Qualitative calls
- Weekly priority emails from fhi360 to sites
 - Collating protocol team priorities
- Listservs
 - Cross-site communications/sharing
- FHI360 Site assessment visits
- Patrick Ndase, MTN Regional Physicians site visits



Future

We are all in this together

- We all work together – all parts of the study are all our business

Recruitment

Retention

Adherence

Sample collection

Staff morale

Community/outreach

Communications

Lab quality

QC/QA

Regulatory

Safety Monitoring

Space/facilities

Study drug/pharmacy

Contraception

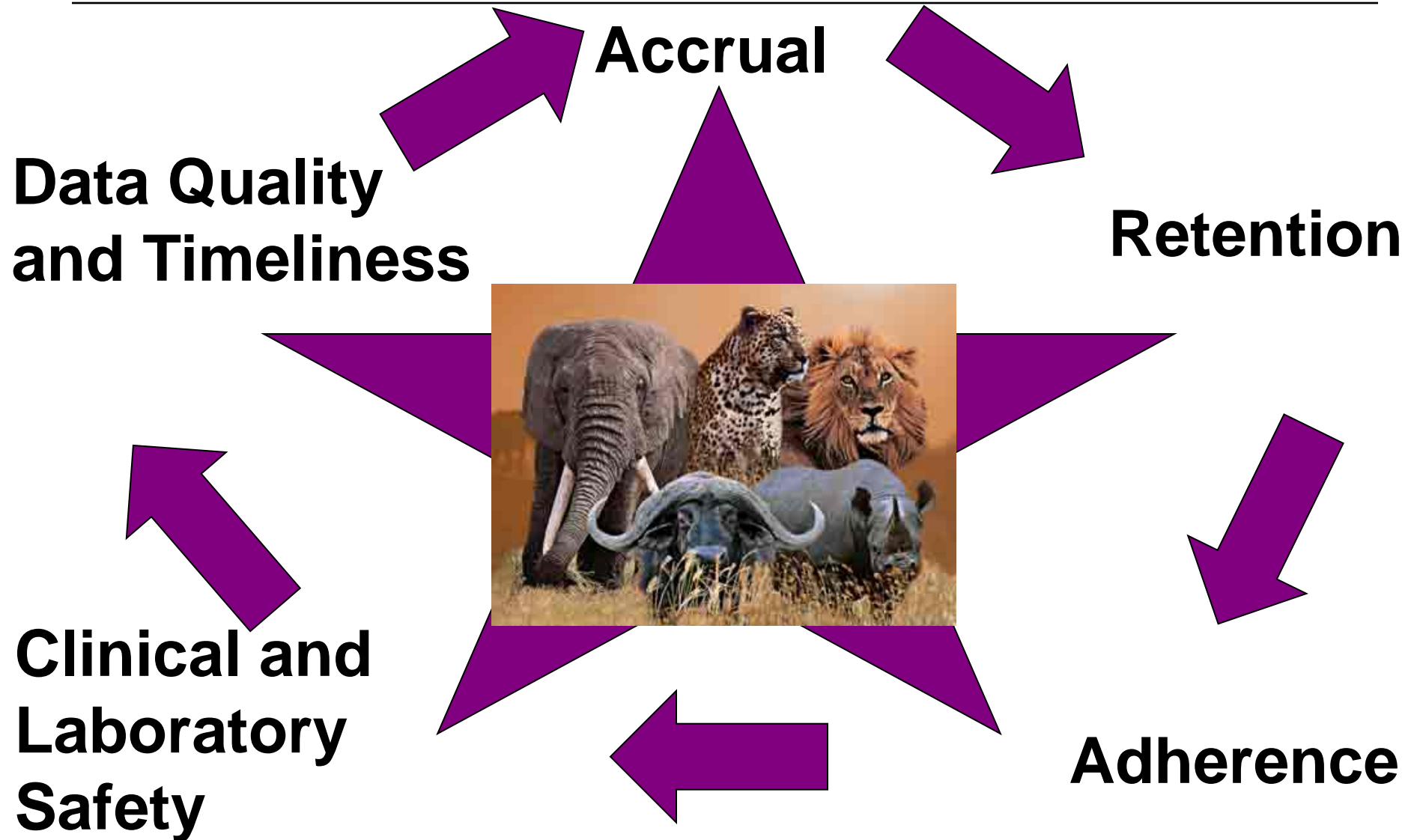
Lab-clinic interface

Monitoring follow-up

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The Big Five



End of enrollment

- ASPIRE protocol planned to enroll approximately 3476 women, anticipating a background HIV incidence of 3.9% per year
 - With at least 120 HIV seroconversions required to assess HIV protection with confidence & goal of ≥ 12 months of safety per participant
- Recent data (VOICE, FEM-PrEP) have demonstrated that HIV incidence is, unfortunately, higher than 3.9% per year in several settings; in addition, ASPIRE enrollment has been >1 y
 - Thus, fewer than 3476 enrollees may be necessary. *Note: this does not imply anything (+ or -) about ring effectiveness in the trial.*
 - We anticipate that the current site targets will be sufficient. To confirm with SMC & DSMB in May.
 - End of enrollment = Q2 2014!

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- **May 2014**
 - **5th = SMC, 29/30 = DSMB**

Timeline

2011

- Initiate site IRB and regulatory approval process

2012

- IRB/regulatory approvals, trainings, start

2013

- Enrollments, follow-up

2014

- End of enrollment, continue follow-up

2015

- Completion of follow-up, results

Retention from day 1 to day X

- ASPIRE is a many-month, multi-hour commitment
 - We have amazing retention now
 - Trust the teams, keep your enthusiasm
 - Team call : Off-site visits to ensure retention and adherence

- How can we continue to create cultures that make sites places where participants want to spend several hours each month? (and staff each day of each month)
 - Team call : Addressing participant fatigue

Adherence monitoring in MTN-020

- Monthly shipping, testing, and review of plasma dapivirine data, according to a pre-defined plan
- Information is reviewed by-site, rather than by-subject, preserving blinding. MOCK example:

SITE	% SAMPLES WITH DAPIVIRINE	ADHERENCE ESTIMATE = middle column x 2 (since ½ expected placebo)
1	50	100
2	48	96
3	40	80



Adherence monitoring in MTN-020

- Monthly shipping, testing, and review of plasma dapivirine data, according to a pre-defined plan
- Information is reviewed by-site, rather than by-subject, preserving blinding.
- Results? *We are optimistic!*

Accrual→Retention→Adherence→Safety→ Quality

- Smart accrual
- High retention
- Motivated adherence (engagement)
- 100% attention to data quality & participant safety

Everything else flows from these



ASPIRE ...

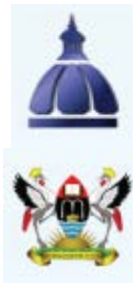
ONE CHANCE

OUR CHANCE

IT TAKES A TEAM



Malawi College of
Medicine – JHU
Research Project



UNC Project -
Malawi



INTERNATIONAL
PARTNERSHIP FOR
MICROBICIDES



University of Zimbabwe,
School of Medicine



DESMOND TUTU
HIV FOUNDATION