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Swiss Tropical and Public Health Institute
Schweizerisches Tropen- und Public Health-Institut
Institut Tropical et de Santé Publique Suisse
Associated Institute of the University of Basel

Controlled human malaria infection (CHMI) in Africa using Sanaria® PfSPZ Challenge:

Introducing a powerful new research tool for evaluating antimalarial drugs and vaccines and for elucidating malaria biology

IABS 2nd Human Challenge Trials Conference- September, 2017

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Evaluation for Malaria Intervention Efficacy

http://in-control.entriforccm.eu/chapters/chapter-5/staying-healthy/

Exposure to natural transmission

- Potentially better predictor of efficacy since mosquitoes harbor heterogeneous populations of *P. falciparum*
- Requires areas of high malaria attack rate

Controlled human malaria infection (CHMI)

- Efficacy of a vaccine or product can be determined in a matter of weeks
- Thus informing programs of the desirability of going further to field studies and/or vulnerable populations

Public health and industry: Clinical development plan acceleration

CHMI - Mosquito Bite Versus Injection by Needle and Syringe

SANARIA
MALARIA ERADICATION THROUGH VACCINATION

Injection of Aseptic, Purified, Cryopreserved *P. falciparum* Sporozoites (PfSPZ Challenge): An Alternative to Mosquito Bites for Controlled Human Malaria Infection

TL Richie[1], PF Billingsley[1], BKL Sim[1], ER James[1], A Richman[1], T Li[1], A Eappen[1], E Bijker[2], M Roestenberg[2], KE Lyke[3], M Laurens[3], C Daubenburger[4], B Mordmüller[5], GP Gómez-Pérez[6], A Legarda[6], S. Shekalaghe[7], S Hodgson[8], AV Hill[8], E Juma[9], C Plowe[3], B Ogutu[9], B Lell[10], K Marsh[8,9], P Alonso[6], S Abdulla[7], P Kremsner[5], M Tanner[4], RW Sauerwein[2], SL Hoffman[1]

1. Sanaria Inc. USA; 2. RUMC, Netherlands; 3. University of Maryland, USA; 4. Swiss TPH, Switzerland; 5. University of Tübingen, Germany; 6. CRESIB, Spain; 7. Ifakara Health Institute, Tanzania; 8. University of Oxford, UK; 9. KEMRI, Kenya; 10. CERMEL, Gabon

Annual Meeting of the American Society for Tropical Medicine and Hygiene, New Orleans, 2-6 Nov, 2014

Comparison of CHMI by Mosquito Bite and PfSPZ Challenge

	Logistics	Safety	Geographic Limitations	Quality Control	Variability
Mosquitoes	• Infected mosquitoes production must be synchronized with CHMI: insectary and parasite culture facilities may need to be in continuous production mode. • Mosquitoes available for CHMI only for 5-7 days or additional lots of mosquitoes required. • Mosquito shipping to CHMI site requires careful packaging and permits. • CHMI site requires facilities, equipment and mosquito-experienced personnel.	• Infected mosquitoes have unique safety issues from time of feeding, through to shipping, and holding and use for CHMI. • Accidental release at CHMI site could halt the study and puts staff and volunteers at risk. • CHMI sites requires a minimum safety infrastructure and extensive training of staff in emergency responses. • Mosquito bites can induce significant wheal and flare reactions	• *A. stephensi*, the mosquito of choice for CHMI, is an Asia-Pacific mosquito. • *A. stephensi* has been adapted into laboratory colonies in Europe and North America. • Shipping to places where it could become an invasive malaria vector is problematic or not permitted. • The 'gold standard' mosquito CHMI is restricted to the mosquito's current range and labs in temperate locations.	• QC of infected mosquitoes for CHMI is extremely limited. • Upstream, QC is checking of reagents, assessment of parasite cultures and oocyst infections, then checking for PfSPZ in the salivary glands. • In-process QC problems can compromise a study, requiring the production of back-up lots. • Mosquito bite CHMI studies are characterized by massive over-production of infected mosquitoes.	• Lot-to-lot variability of infected mosquitoes can be minimized rather than controlled. • Even within a single lot of mosquitoes, there can be significant variability in prevalence and intensity of PfSPZ infections. • Shipping of mosquitoes can have variable effects upon their behavior while mosquitoes will respond variably to different volunteers.
PfSPZ Challenge	• Infected mosquitoes production independent of CHMI date. • PfSPZ Challenge available at all times – lots stable for years. • Shipping to CHMI site requires standard dry shipper. • CHMI site currently requires Biological Safety Cabinet.	• Safety issues are standard (liquid nitrogen handling, needle stick). • No accidental release possible. • No requirement for specialist safety infrastructure. • Injection site has little or no reactogenicity.	• No geographic limitations on where CHMI by PfSPZ Challenge can be conducted. • PfSPZ Challenge already used successfully in 3 countries in Africa.	• Extensive QC of PfSPZ Challenge. • In-process QC problems will not affect the study because timing of production is independent of CHMI date. • Material can be QC tested with range of safety tests after production and before use. • Controlled production.	• Multiple CHMIs with same lot. • Precise dose can be formulated and administered, so there is less variance in pre-patent period; sequential CHMI's comparable. • Shipping is tightly controlled and has no effect on PfSPZ.

2014 – 2016 Profile is the same

2014 -2016 Significant Improvement

Why CHMI Trials in Africa?

CHMI Studies Africa 50's - 60's

Br Med J. 1954 Feb 6;1(4857):290-4.

Protection afforded by sickle-cell trait against subtertian malareal infection.

ALLISON AC.

Riv Malariol. 1962 Dec;41:199-210.

The inoculation of semi-immune Africans with sporozoites of Laverania falciparum (Plasmodium falciparum) in Liberia.

BRAY RS, GUNDERS AE, BURGESS RW, FREEMAN JB, ETZEL E, GUTTUSO C, COLUSSA B.

West Afr Med J. 1963 Aug;12:141-73.

A LONGITUDINAL LONGITUDINAL SURVEY OF NATURAL MALARIA INFECTION IN A GROUP OF WEST AFRICAN ADULTS. I.

BRUCE-CHWATT LJ.

CHMI Studies Africa Modern era

CHMIs are commonly performed in malaria Naïve population

- Expense of mosquito colony and Logistics with *An. stephensi* importation
- Only a small number of research centers have the facilities required to perform mosquito based CHMI studies
- Uncertainty about GCP

A proper modern CHMI study would help to investigate potential correlates of NAI

Validation of proposed in vitro measures of NAI such as growth inhibition antibody activity (GIA) and antibody-dependant cellular assays

Malaria is a significant health problem in African, research institutions should be empowered to study it with full set of research tools

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Optimization of Dose and Route for Controlled Human Malaria Infection (CHMI)

PfSPZ Based - Controlled Human Malaria Infection (CHMI):

aseptic, purified, cryopreserved, infectious Plasmodium falciparum (Pf) sporozoites (SPZ)

(by Sanaria Inc.)

Opened the potential for CHMI to be done in any research facility set up for malaria clinical trials, including sites to which transport of mosquito is difficult or impossible

- Series of clinical trials from 2010 to 2014
- Ifakara Health Institute (IHI), Bagamoyo, Tanzania
  - First to administer PfSPZ-CHMI and reproduced the infectivity and prepatent period of five PfSPZ-infected mosquitoes and infectivity rates in Africa
  - First to do PfSPZ-CHMI to measure the efficacy of a malaria vaccine in Africa

ASTMH AMERICAN SOCIETY OF TROPICAL MEDICINE & HYGIENE
THE AMERICAN JOURNAL OF TROPICAL MEDICINE AND HYGIENE
official Journal of the American Society of Tropical Medicine and Hygiene

Am J Trop Med Hyg. 2014 Sep 3; 91(3): 471–480. PMCID: PMC4155546
doi: 10.4269/ajtmh.14-0119

Controlled Human Malaria Infection of Tanzanians by Intradermal Injection of Aseptic, Purified, Cryopreserved *Plasmodium falciparum* Sporozoites (Shekalaghe et. al)

Dose response was seen after DVI and IM adminsitration, but not ID administration

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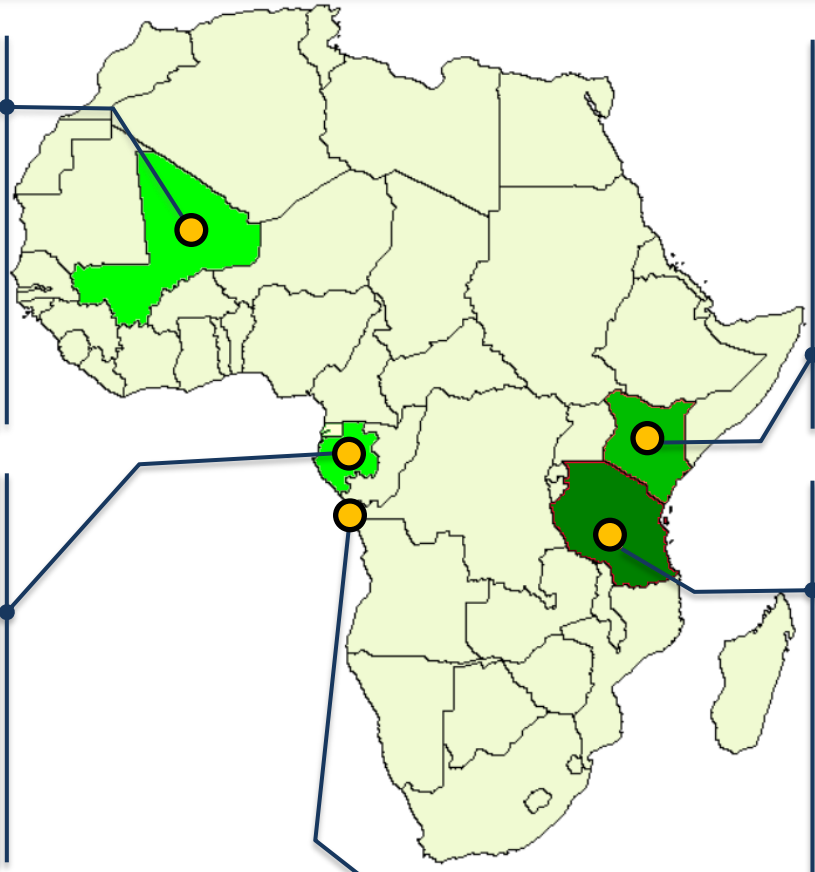
Application: PfSPZ-CHMI in Africa



Number of studies in which CHMI was performed with or without Vaccination

Mali
- 2014; CHMI: 45 subjects — VE

NF54

Kenya
- 2013; KSPZC1: 28 subjects — MI
- 2016; CHMI: 37 subjects — MI
- 2017; CHMI: 64 subjects — MI

NF54

Gabon
- 2014; CHMI: 25 subjects — MI
- 2015; GMZ2-CAF01: 35 subjects — VE

NF54

Tanzania
- 2012; BSPZC1: 24 subjects — MI
- 2015; BSPZV1: 64 subjects — VE
- 2016; BSPZV2: 24 subjects — VE

Upcoming 2018
- BSPZV3 CHMI in HIV+ve — VE
- MalHerbal — DE

NF54

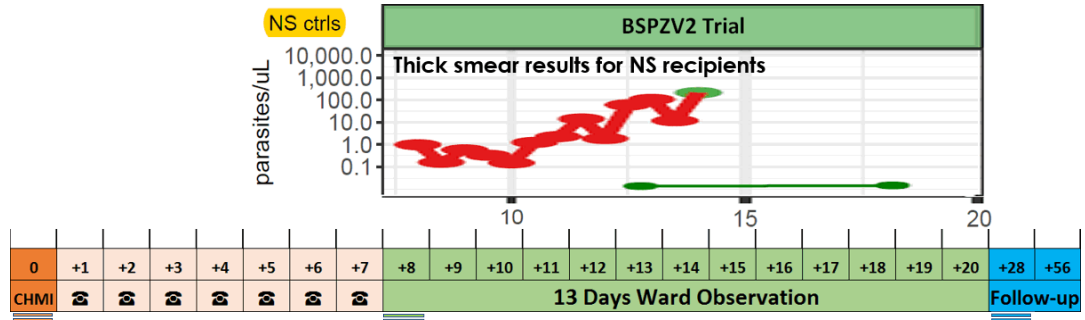
Equatorial Guinea
- 2017; EGSPZV2: 45 subjects — VE

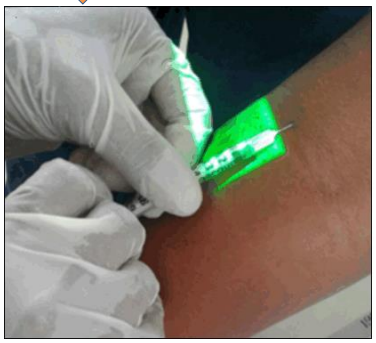
NF54

MI Malaria Infectivity Study
VE Vaccine Efficacy Study
DE Drug Efficacy Study

Application: PfSPZ Standard CHMI Model in Tanzania

Pre-CHMI Assessment



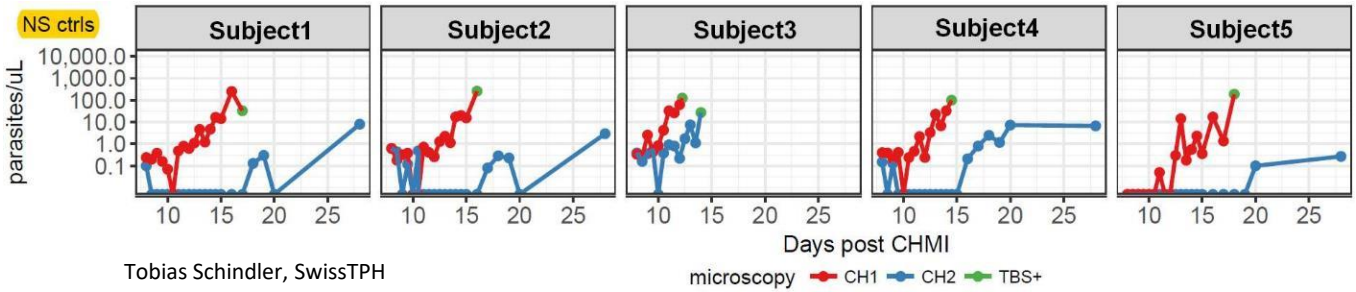


Boosting effect of CHMI in malaria pre-exposed adult volunteers

During the 28 day **Post-CHMI**	Results			
	CHMI #1		CHMI #2	
	TBS	qPCR	TBS	qPCR
Normal Saline (NS) Placebo Controls	⊕	⊕	⊖	⊕
	⊕	⊕	⊖	⊕
	⊕	⊕	⊕	⊕
	⊕	⊕	⊖	⊕
	⊕	⊕	⊖	⊕

First CHMI: 5/5 volunteers: Positive TBS by microscopy

Second CHMI, 4/5 volunteers: remained negative by TBS, but were identified as malaria positive by qPCR



Tobias Schindler, SwissTPH

Significant boost of acquired immunity as indicated by a significant delays to PCR positivity

CHMI studies in Tanzanian volunteers provides a unique tool to identify immune effector mechanisms under highly controlled conditions.

Application: CHMI with homologous PfSPZ Challenge

- **May be a more rigorous assessment of vaccine efficacy than natural exposure to heterogeneous Pf in the field**

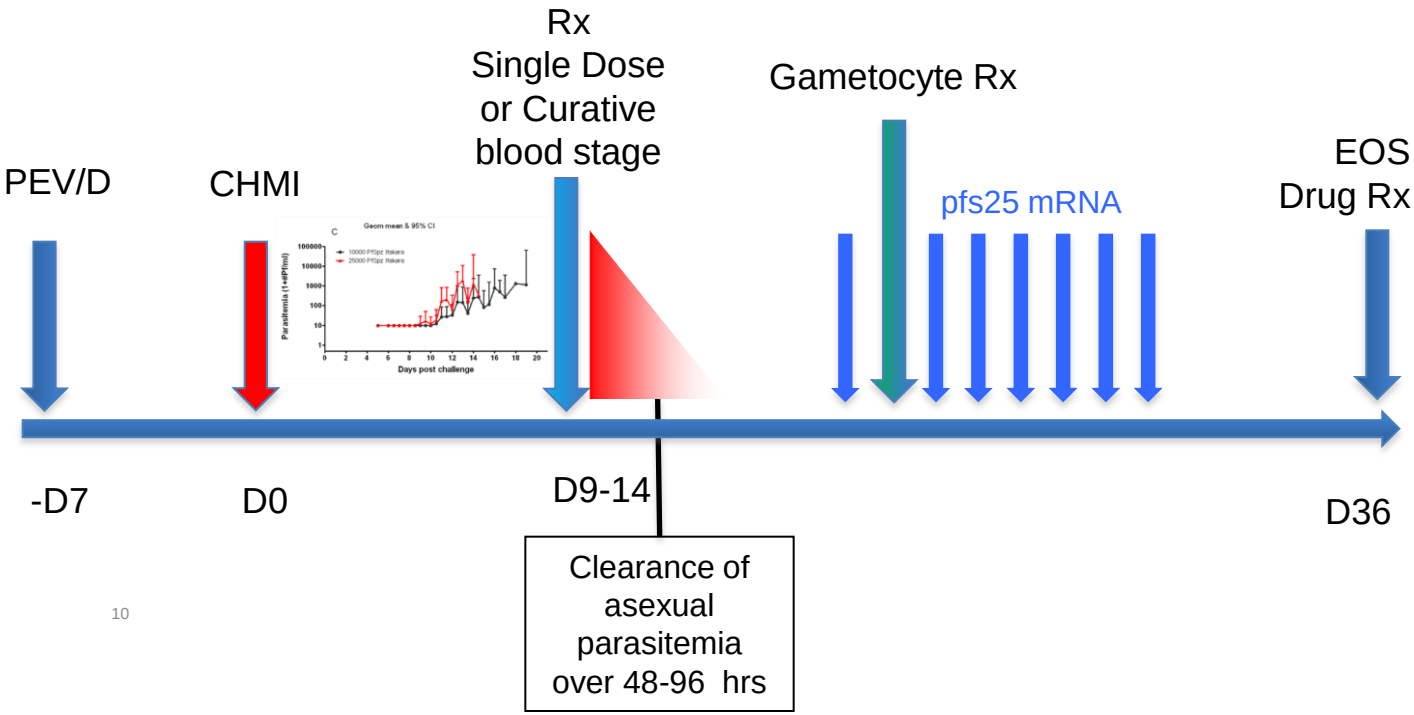
5 doses of 2.7 x 10^5 PfSPZ of PfSPZ Vaccine in Malian adults

- ❖ Follow up for 24 weeks in face of intense natural exposure to Pf (Sissoko et al., *Lancet ID, 2017*)
  - Infection rate in controls of **93%**
  - Protective efficacy of 52% by time to event analysis and 29% by proportional analysis

5 doses of 2.7 x 10^5 PfSPZ of PfSPZ Vaccine in Tanzanian adults

- ❖ CHMI with 3,200 PfSPZ of PfSPZ Challenge (NF54) at 3 weeks and at 24 weeks (Jongo et al., *submitted for publication*)
  - Infection rate in controls of **100%**
  - Protective efficacy of 20% at 3 weeks and all protected at 24 weeks

Application: CHMI Model; Drug, Vaccine and Transmission Studies

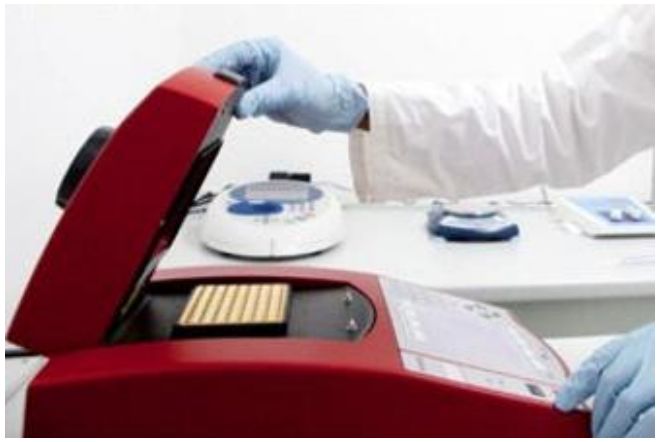


Safety: Detection of Parasitemia

BS and Microscopy

- Still a "Gold Standard"
- SOP for microscopy reading should be similar across sites
- Uniformity in reading expertise - Training

qPCR Based Parasite Detection



- Useful tool but not widely used
- Issues with logistics and practical implementation
- Validation can be potentially expensive and time consuming process

Practical Experience from Bagamoyo:

Samples were measured in real-time (last sample at last day of CHMI)

Safety: Treatment after CHMI

- Currently treatment is based on thick blood smear
  - standardized case definition for positivity
- Mitigation of potential risks involved with introducing exogenous CHMI strains to local community
  - Presumptive treatment at +28 days after CHMI for those remaining negative
  - Treatment based on PCR??
- Treatment guidelines across countries differ significantly
  - Challenging to decide on a single quick, effective treatment eg. Though NF54 is sensitive to chloroquine, it's not in the treatment guidelines
- Drugs have their own side effects
  - Calls for uniform attribution criteria

Collaborations and Networking

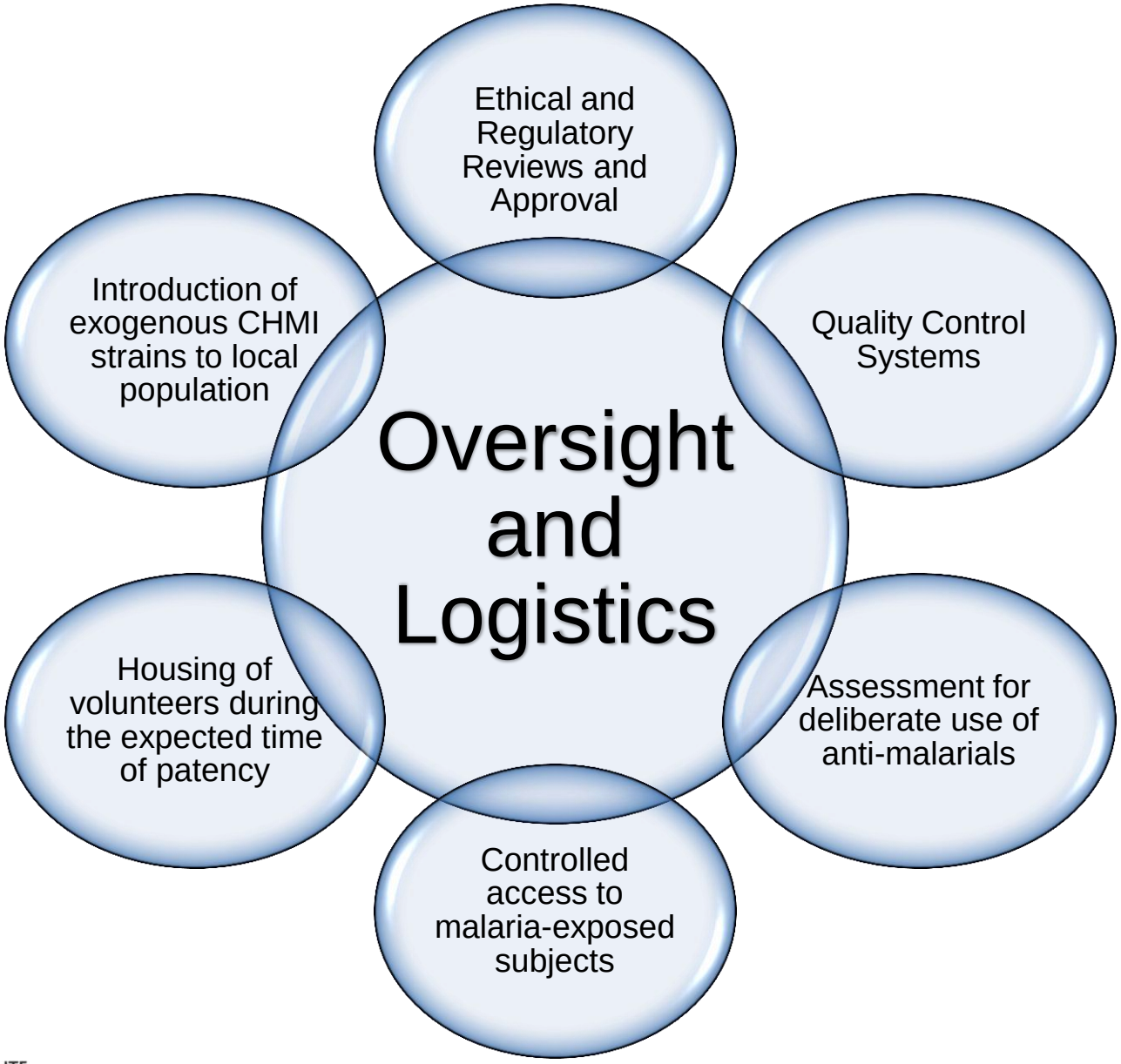
MILESTONES ACHIEVED IN EG BY IHI TEAM WORKING WITH PARTNERS FROM EG MOH, SWISS TPH, MCDI AND SANARIA

- **Capacity Building**
- **First ever regulatory and clinical trial ethical approval system in the history of a country**
- **First ever clinical trials conducted including CHMIs**

We are extremely Proud of this South-South Collaboration

IHI

Safety: Oversight and Logistics for Provision of Live Parasites



Perspective

- Efficacy evaluation of Sanaria® PfSPZ Vaccine by CHMI with Sanaria® PfSPZ Challenge in people living with HIV at BCTU in Bagamoyo

- CHMI Modal - Testing of herbal products for malaria intervention in Bagamoyo Tanzania