Research in Africa and the Middle East: Regulatory, Legal and Ethical Perspectives

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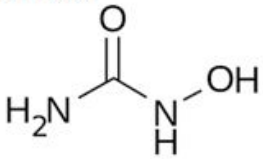
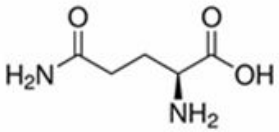
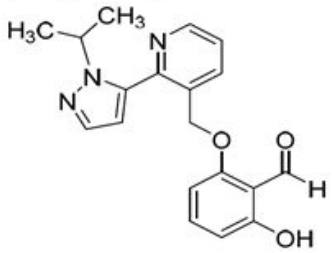
Disclosures

- Novartis inevestigator ad-board
- GBT research Speaker
- Vertex therapeutics DSC
- Terumo Speaker
- Amgen Speaker
- Takeda Speaker

Agenda

- Background
- Summary of successful trials
- Regulatory frame work
- Unmet needs
- Networks
- Investigators Duties
- Conclusions

Approved Therapies in SCD

Compound	Company	Structure	Mechanism of Action	Formulations	Indication
Hydroxyurea	Numerous	Hydroxycarbamide $CH_4N_2O_2$ 	An antineoplastic agent that inhibits DNA synthesis through the inhibition of ribonucleotide diphosphate reductase. Hb F Induction, reduces inflammation and hemolysis	Capsules: Hydrea and Droxia; 100, 200, 300, 400, 500 mg Tablets: Siklos; 100 mg, 1000 mg Solution 100 mg/ml or higher as needed	Sickle cell anemia; Myeloproliferative disorders, certain cancers
L-Glutamine (Endari)	Emmaus Medical Inc.	2-Amino-4-carbamoylbutanoic acid 	Not well known. It may improve the NAD redox potential in sickle RBCs through increasing the availability of reduced glutathione.	Powder in packets containing 5g each	Reduction of the acute complications of sickle cell disease in adult and pediatric patients 5 years of age and older
Crizanlizumab-tmca	Novartis	Monoclonal antibody	Anti-P-selectin	Intravenous solution	Reduces the frequency of VOCs in adults and pediatric patients aged 16 years and older
Voxelotor (Oxbryta, GBT440)	Global Blood Therapeutics Inc	Benzaldehyde, 2-hydroxy-6-((2-(1-(1-methylethyl)-1H-pyrazol-5-yl)-3-pyridinyl)methoxy) 	Hb S Polymerization inhibitor	Tablets (500 mg) for oral use	Treatment of sickle cell disease in adults and pediatric patients 12 years of age and older

Mediterr J Hematol Infect Dis. 2020 Jan 1;12(1):e2020010. doi

Ongoing and Potential Trials

able 4. Potential drug therapies for the management of SCD.

Compound	Company	Structure	Indication	Stage of Development	Mechanism of Action
Decitabine	Astex Pharmaceuticals	5-aza-2'-deoxycytidine	Myelodysplastic syndrome, SCD	Phase II study completed for SCD	DNA methylase inhibitor, Hb F induction
Sodium butyrate	Sigma Aldrich	$C_4H_7NaO_2$	Inhibit tumor cell growth, SCD	No current studies being conducted in relation to SCD	Hb F induction
Pomalidomide	Celgene Corporation	$C_{13}H_{11}N_3O_4$	GvHD versus host disease, myelofibrosis, scleroderma and idiopathic pulmonary Fibrosis, SCD	Phase I study completed for SCD	Hb F induction
Panobinostat	Novartis	(2E)-N-Hydroxy-3-[4-[[2-(2-methyl-1H-indol-3-yl) ethyl]amino]methyl]phenyl]-2-propenamide	Treatment of multiple myeloma and other cancers, SCD	Phase I for SCD	Hb F induction
Intravenous Ig	GRIFOLS BIOLOGICALS, Inc.	$C_{6112}H_{9588}N_{1688}O_{1968}S_{48}$	Plasma protein replacement Therapy, SCD	Recruiting for Phase I/II for SCD	Inhibits cellular adhesion
Low-molecular weight heparin	Sanofi	$(C_{12}H_{21}NO_{19}S_3)_n$	Deep vein thrombosis, Myocardial infarction, unstable angina, SCD	Phase II for SCD	Inhibits cellular adhesion
Dalteparin	Pfizer	2-O-sulpho-α-L-idopyranuronic acid structure at the nonreducing end and a 6-O-sulpho-2,5-anhydro-D-mannitol structure at the reducing end of their chain	Acute venous thromboembolism, SCD	Phase II completed for SCD	Inhibits cellular adhesion
SelG1 (Crizanlizumab)	Selexys Pharmaceuticals, Now Novartis	Humanized P-selectin antibody	VOCs in children and adults with SCD	Scentsin Trial Phase II completed for VOC, Four other trials are ongoing	Inhibits cellular adhesion
Propranolol	Forest Laboratories	2-Propanol, 1-[(1-methylethyl) amino]-3-(1-naphthalenyloxy)	Hypertension, SCD	Phase II completed for SCD	Inhibits cellular adhesion
Regadenoson; Adenosine 2A receptor antagonist	Gilead Sciences	1-(6-Amino-9-β-D-ribofuranosyl-9H-purin-2-yl)-N-methyl-1H-pyrazole-4-carboxamide	Vasodilator	Phase II completed for SCD	Anti-inflammatory Agents
NKTT120	NKT Therapeutics	Humanized antibody to iNKT	Rapid and sustained iNKT cell depletion in adults with SCD	Phase I study for SCD completed	Reduce chronic inflammation associated with SCD
Atorvastatin Statins	FA Davis	$(C_{33}H_{34}FN_2O_5)_2Ca \cdot 3H_2O$	Improves endothelial dysfunction in SCD with nephropathy	Phase II trial has just been completed	3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor
Zileuton	Abbott Laboratories and now Cornerstone Therapeutics Inc.	$C_{11}H_{12}N_2O_2S$	Approved for the prophylaxis and treatment of chronic asthma for patients who are age 12 and older. Beneficial in SCD animal model	Phase I trial completed	Inhibits 5-lipoxygenase, a potent inflammatory leukotriene
N-acetyl cysteine	Galleon Pharmaceuticals	L-Cysteine, N-acetyl $C_5H_9NO_3S$	Rad chemotherapy-induced mucositis; Radiochemotherapy induced injury, bone marrow, thrombocytopenia; sepsis, SCD	Phase III for SCD completed	Anti-inflammatory Agent, reduces oxidative stress in sickle cell patients
α-Lipoic acid	Meda Biotech Inc.	1,2-Dithiolane-3-pentanoic acid $C_8H_{14}O_2S_2$	Diabetic neuropathy, SCD	In an open randomized trial, the ALA dose used was not effective to prevent oxidative damage in patients with SCD	Anti-inflammatory and anti-oxidant agent
Canakinumab	Novartis	Canakinumab is a recombinant, human anti-human-IL-1β monoclonal antibody that belongs to the IgG1/κ isotype subclass	For Familial Cold Autoinflammatory Syndrome (FCAS), Muckle-Wells Syndrome (MWS) and SCD	Phase II ongoing	Anti-inflammatory
Ambrisentan	Augusta University with Gilead Sciences and NHLBI as collaborators	Endothelin Receptor antagonist (ERA)	Determination of its safety and tolerability in treating SCD	Phase I	Anti-inflammatory, analgesic and improves pulmonary blood low
Rivaroxaban	Bayer	5-Chloro-N-[(5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl]methyl] thiophene-2-carboxamide	For treatment of thrombosis including stroke, prevent VOC	Phase I for SCD completed	Direct oral anti-coagulant

Arginine	Numerous companies produce since this is a vitamin supplement	2-Amino-5 guanidinopentanoic acid	Chest pain, high blood pressure and peripheral arterial disease, SCD	Phase III study for SCD completed in Brazil. Phase II study for SCD completed in US. Another Phase II study for SCD is recruiting in the US.	Vasodilatation
Inhaled Nitric Oxide (NO) in the ED	INO Therapeutics	:N≡Ö:	Therapeutic for VOC in the ED	double-blind, randomized, placebo controlled clinical trial	Vasodilatation
PF 04447943	Pfizer	6-[(3S,4S)-4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	Evaluate change from baseline in potential SCD-related biomarkers	Phase 1b for patients with SCD completed	Vasodilatation; Phosphodiesterase 9A inhibitor
IMR-687	Imara Inc	6-[(3S,4S)-4-Methyl-1-(2-pyrimidinylmethyl)-(3-pyrrolidinyl]-3-(tetrahydro-2H-pyran-4-yl)triazolo[1,5-a]pyrazin-8(7H)-one Molecular formula C21 H26 N6 O2	SCA (Homozygous Hb SS or Sickle-β0 Thalassemia)	Phase 1a completed. Phase 2a is recruiting with an open extension study	Phosphodiesterase inhibitor with multimodal mechanism of action: Vasodilatation Inhibition of white blood cell adhesion Increase Hb F level
Riociguat	Bayer	Methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-pyrimidinyl(methyl) carbamate	Multicenter study in patients with SCD	Phase 2 multi-center, randomized, double-blind, placebo-controlled, parallel groups study. Recruiting	Riociguat is a stimulator of soluble guanylate cyclase (sGC), an enzyme in the cardiopulmonary system and the receptor for NO resulting in vasodilatation
Olinciguat (IW-1701)	Ironwood, Cyclerion Therapeutics	Olinciguat;UNII-PD3F4ZXD02 $C_{21}H_{17}FN_4O_3$	Patients with SCD	STRONG SCD to evaluate the safety and tolerability of different dose levels in SCD patients. Recruiting	Stimulates guanylate cyclase (sGC), known to play a key role in the production of nitric oxide. Vasodilatation
Voxelotor (GBT-440)	Global Blood Therapeutics Inc	Benzaldehyde, 2-hydroxy-6-[[2-(1-(1-methylethyl)-1H-pyrazol-5-yl)-3-pyridinyl]methoxy]	Prevention of VOCs and treatment of other complications	After successful phase I and II trials, Phase 3 HOPE trial Voxelotor significantly increased Hb levels compared to placebo and reduced markers of hemolysis. Exploratory post-hoc trial showed that Voxelotor resolved or improved leg ulcers in some patients.	Inhibition of Hb S polymerization. Increases the affinity of Hb S to oxygen
FT-4202 Pyruvate Kinase Activator (PKR)	Forma Therapeutics, Inc.; Medpace, Inc.	An oral small-molecule agonist of pyruvate kinase red blood cell isozyme (PKR)	Treatment of hemolytic anemias	Phase 1	Agonist of pyruvate kinase enzyme
Niacin (Vitamin B3)	AbbVie Ltd	$C_6NH_5O_2$	Reduces risk of heart disease, improves blood flow in people with SCD	Phase II study completed for SCD	Increases levels of HDL and improves blood flow
Cholecalciferol (Vitamin D3)	Numerous companies	25-Hydroxyvitamin D_3	Vitamin supplement, SCD	Phase study with adult patients with SCD completed. Phase I and II completed with pediatric patients with SCD. Phase III for pediatric patients with SCD not yet recruiting	Supplementary vitamin

ADP: Adenosine diphosphate; ED = Emergency department; Hb: Hemoglobin; HDL = High-density lipoproteins; kDa: Kilodalton; NO: Nitric oxide; RBC: Red blood cell; SCA: Sickle cell anemia; SCD: Sickle cell disease; VOCs: Vaso-occlusive crises.

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Discontinued or Terminated Trials

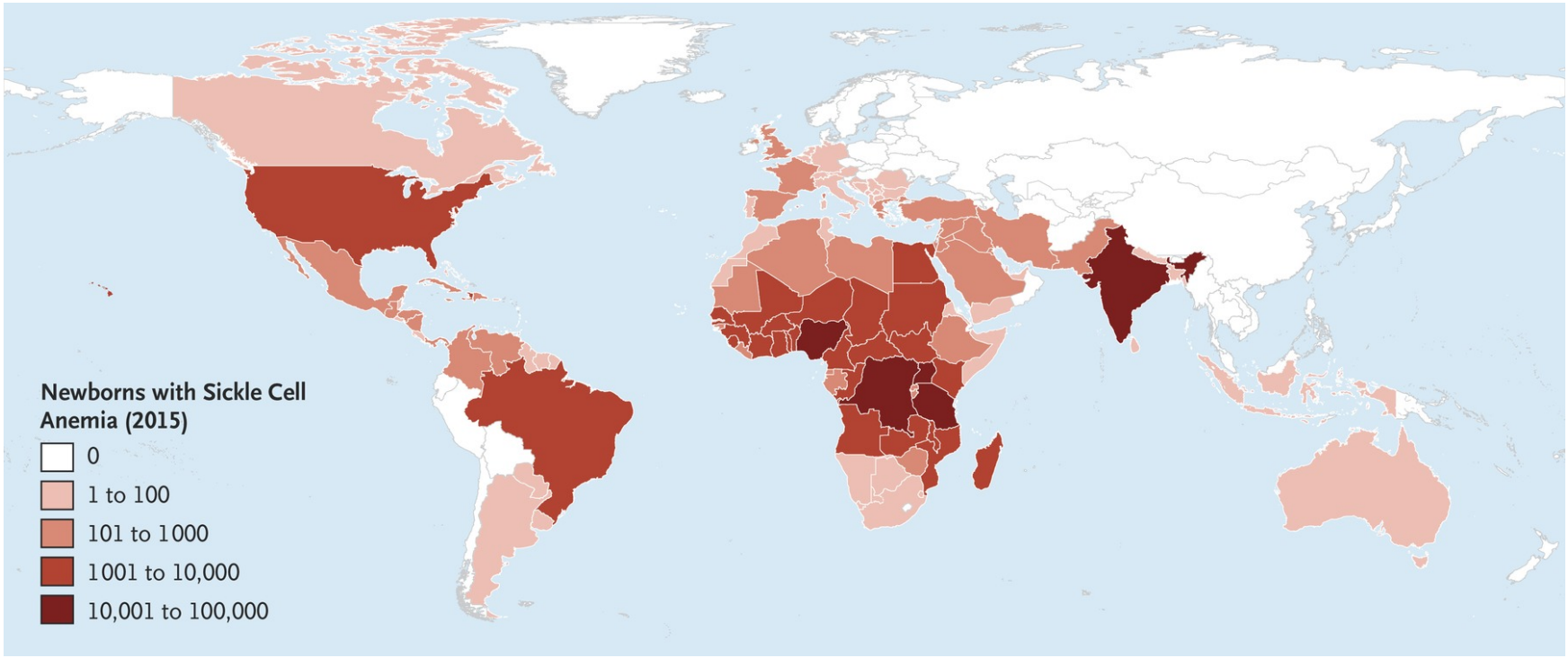
Table 3. Completed multicenter randomized double-blind placebo-controlled trials to prevent or treat sickle painful crises that failed, discontinued or terminated.

Compound	Company	Mechanism of Action	Indication	Stage of Development	Reference
Acetylsalicylic acid	Takeda	Benzoic acid, 2-(acetyloxy)-	General pain and thrombosis, SCD	Phase I and II study for SCD completed	[1]
AES-103	AesRx	Anti-sickling agent	Anemia; SCD	Phase I study for SCD completed. Phase II study for SCD terminated by the Sponsor due to unblinding between study drug and placebo groups at the subject, site and Sponsor levels	[2,3]
Dipyridamole	Boehringer Ingelheim Pharmaceuticals, Inc	RBC hydration	Thrombosis; SCD	Phase II study withdrawn	[4]
Eptifibatide	Millennium and Schering Plough	Antiplatelet agent Use as therapeutic agent for VOC	Acute myocardial infarction, unstable angina, abrupt closure following coronary angioplasty, stroke and other diseases associated with arterial thrombosis; treat VOC	Phase II for SCD terminated due to slow accrual and no cost extension not approved by NHLBI	[5]
HQK 1001	HemaQuest	γ globin gene promoter	SCA and β-Thalassemia	Phase II for SCD terminated	[6]
Inhaled Nitric Oxide (NO)	Ikaria	Vasodilator	Therapeutic for VOC	Phase III for SCD; Failure	[7]
L-citrulline	Aridepion	Vasodilator	Pediatric pulmonary hypertension, post-cardiopulmonary bypass surgery; SCD	Ceased; Phase I for SCD	[8]
Magnesium Sulfate ($MgSO_4$)	Numerous companies produce magnesium as magnesium oxide, magnesium citrate, magnesium sulfate, magnesium gluconate and magnesium pidolate	RBC hydration Therapeutic agent	Vitamin supplement; Treat VOC	Phase II and III for SCD; Failure	[9]
MP4OO	Sangart	Prevents microvascular stasis; Therapeutic agent	Anemia; Treat SCD	Discontinued; Phase I completed. Phase II withdrawn prior to enrollment for SCD	[10,11]
Nonionic polyoxyethylene-polyoxypropylene; Poloxamer 188 (Flocor)	CytRx	Oxirane, methyl-, polymer with oxirane, block, Therapeutic agent	Surfactant	Treat VOCs and ACS in SCD and acute myocardial infarction	[12-13]
Omega-3-acid ethyl esters	Glaxo Smith Kline	Anti-inflammatory agent	Improves several cardiovascular risk factors: lowers serum triglyceride concentration, lowers blood pressure, reduces resting heart rate, improves endothelial dysfunction; SCD	Phase II for SCD terminated due to manufacturing problem with study drug	[15,16]
Prasugrel (DOVE Trial)	Eli Lilly	Inhibition of platelet activation and aggregation	Prevention of VOC	Failure	[17]
Senicapoc	Pfizer	Gardos channel blocker, Preventive agent	Prevention of VOC	Phase II completed for SCD; Drug increased red cell survival and hematocrit and blood viscosity; Phase III trial failed	[18,19]
Sildenafil		Preventive agent	Prevention of VOC	Failure	[20, 21]
Sodium nitrite	Hope	Used to treat cyanide poisoning, Therapeutic agent for leg ulcers	Vasodilator; treat SCD leg ulcers	Phase I and II study for SCD terminated due to low enrollment	[22]
TRF-1101	TRF Pharma	Anti-sickling agent	SCD	Phase I study completed and successfully demonstrated improved microvascular blood flow in patients with SCD and revealed no drug-related side effects. Phase II study terminated due to perceived futility because the baseline pain score in first 40 patients was too low to be able demonstrate improvement.	[23]
Varespladib sodium	Shionogi	Inhibitor of secretory phospholipases A2 (sPLA2)	Therapy for acute chest syndrome in SCA	Discontinued; no current studies being conducted in relation to SCD	[24]
Vepoloxamer 18 (EPIC)	Mast Therapeutics	Similar to Poloxamer 188	Therapeutic for VOC	Failure	[25]
Vorinostat	Merck & Co.	Hb F induction	Cutaneous T-cell lymphoma; SCD	Phase II terminated due to slow accrual	[26]
Sevuparin	Modus therapeutics	Polysaccharide-based drug that is designed to retain the anti-adhesive properties of heparin. Therapeutic agent	Treatment of VOCs	Underwent Phase I and II Trials. Failed to Show Clinically Meaningful Improvements in Managing VOCs.	[27]
Rivipansel sodium, GMI-1070	GlycoMimetics	1,3,6-Naphthalenetrisulfonic acid, 8-[[13-[(1R,3R,4R,5S)-3-[[2-O-benzoyl-3-O-[(1S)-1-carboxy-2-cyclohexylethyl]-_-D-galactopyranosyl]oxy]-4-[(6-deoxy-α-L-galactopyranosyl)oxy]-5-[[(1,2,3,6-tetrahydro-2,6-dioxo-4-pyrimidinyl) carbonyl] amino] cyclohexyl]-	Inflammation and VOCs in SCD. Therapeutic agent	Phase III to treat VOC failed	[28,29]
Sanguinate	Prolong Pharmaceutical	Sanguinate is PEGylated Bovine Carboxyhemoglobin	Designed to prevent clumping of RBC and maintain blood flow. Therapeutic agent	Phase II trial to treat VOC failed	[30]

NHLBI: National Heart, Lung, and Blood Institute; RBC = Red blood cell; SCA = Sickle cell anemia; SCD = Sickle cell disease; VOC: Vaso-occlusive crisis.

Mediterr J Hematol Infect Dis. 2020 Jan 1;12(1):e2020010. doi

Epidemiology of sickle cell disease



Piel F NEJM
Paulukonis, *Public Health Reports* 131:367, 2016

It is estimated that:
•SCD affects approximately 100,000 Americans.
•SCD occurs among about 1/365 Black or African-American births.
•SCD occurs among about 1/16,300 Hispanic-American births.

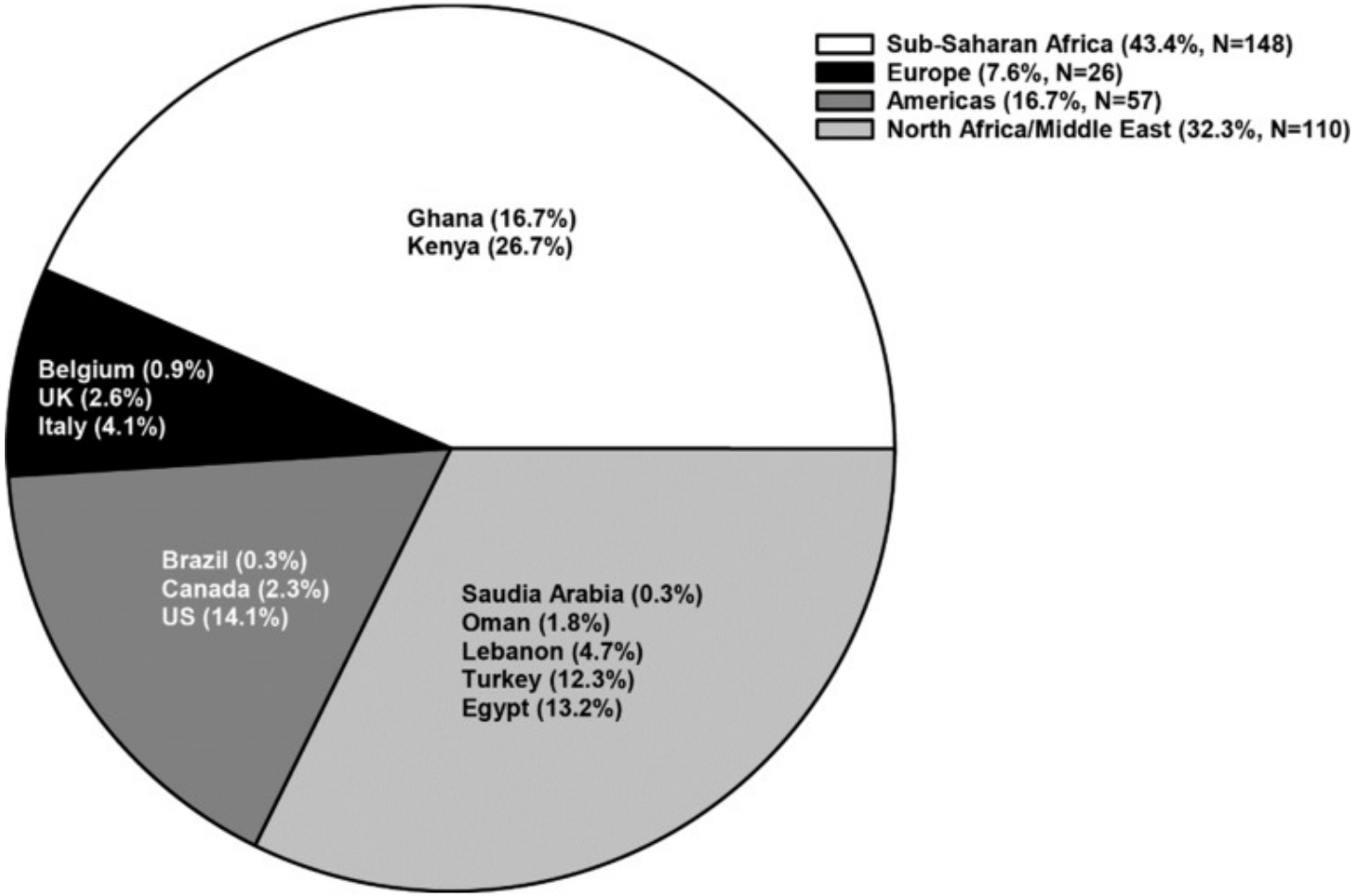
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Multinational Trial of Prasugrel for Sickle Cell Vaso-Occlusive Events

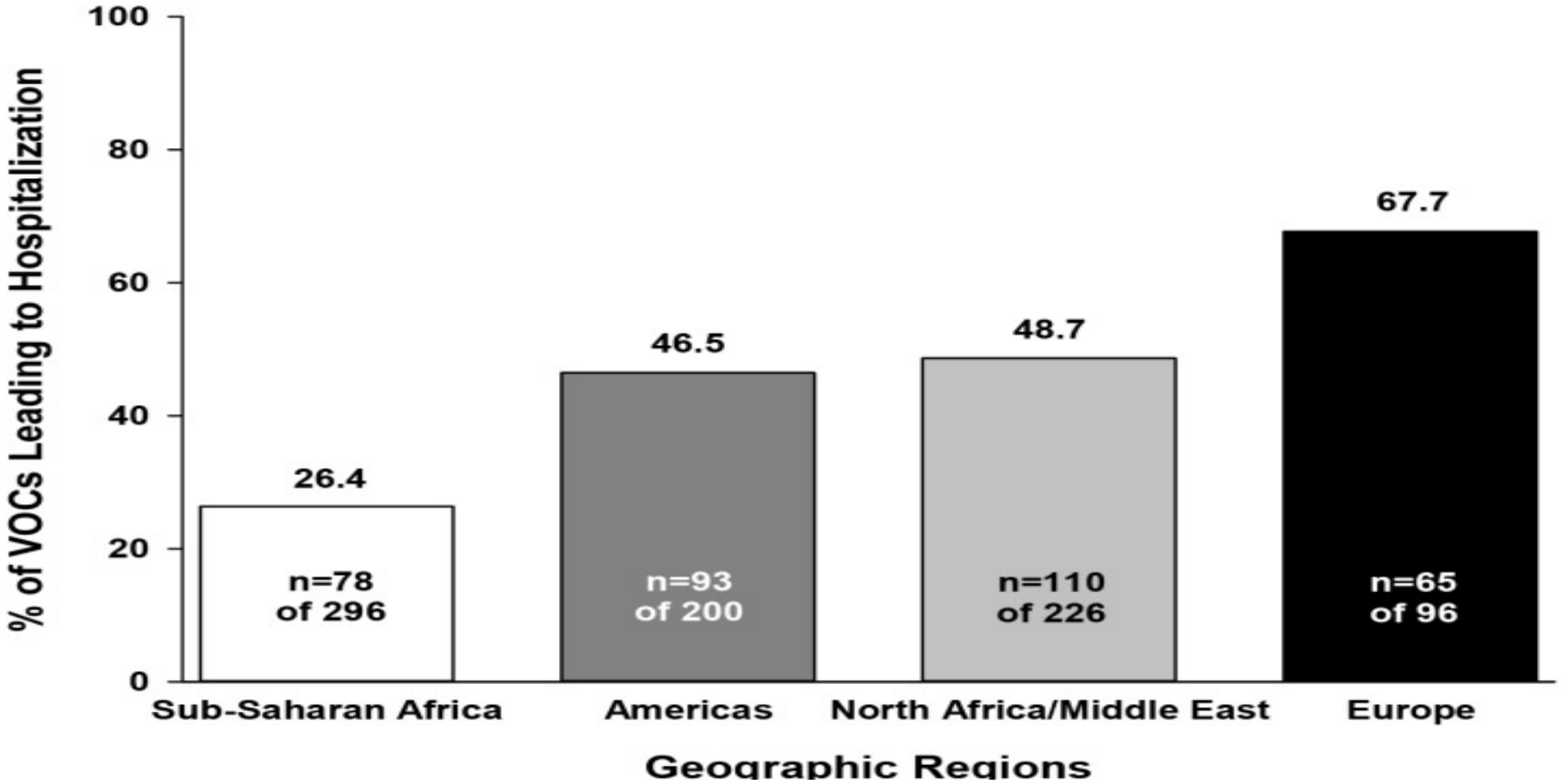
Matthew M. Heeney, M.D., Carolyn C. Hoppe, M.D., Miguel R. Abboud, M.D., Baba Inusa, M.D., Julie Kanter, M.D., Bernhards Ogutu, M.D., Ph.D., Patricia B. Brown, R.N., Lori E. Heath, M.S., Joseph A. Jakubowski, Ph.D., Chunmei Zhou, M.S., Dmitry Zamoryakhin, M.D., Tsiri Agbenyega, M.B., Ch.B., Ph.D., Raffaella Colombatti, M.D., Ph.D., Hoda M. Hassab, M.D., Videlis N. Nduba, M.B., Ch.B., M.P.H., Ph.D., Janet N. Oyieko, M.D., M.Med. (Peds), Nancy Robitaille, M.D., Catherine I. Segbefia, M.B., Ch.B., and David C. Rees, F.R.C.P., for the DOVE Investigators*

Geographic Distribution of Patients in the Dove Trial



Inusa BPD, Colombatti R, Rees DC, Heeney MM, Hoppe CC, Ogutu B, Hassab HM, Zhou C, Yao S, Brown PB, Heath LE, Jakubowski JA, Abboud MR.J Clin Med. 2019 Nov 17;8(11):2009. d

Percentage of vaso-occlusive crises associated with hospitalization during the DOVE study



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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 8, 2019 VOL. 381 NO. 6

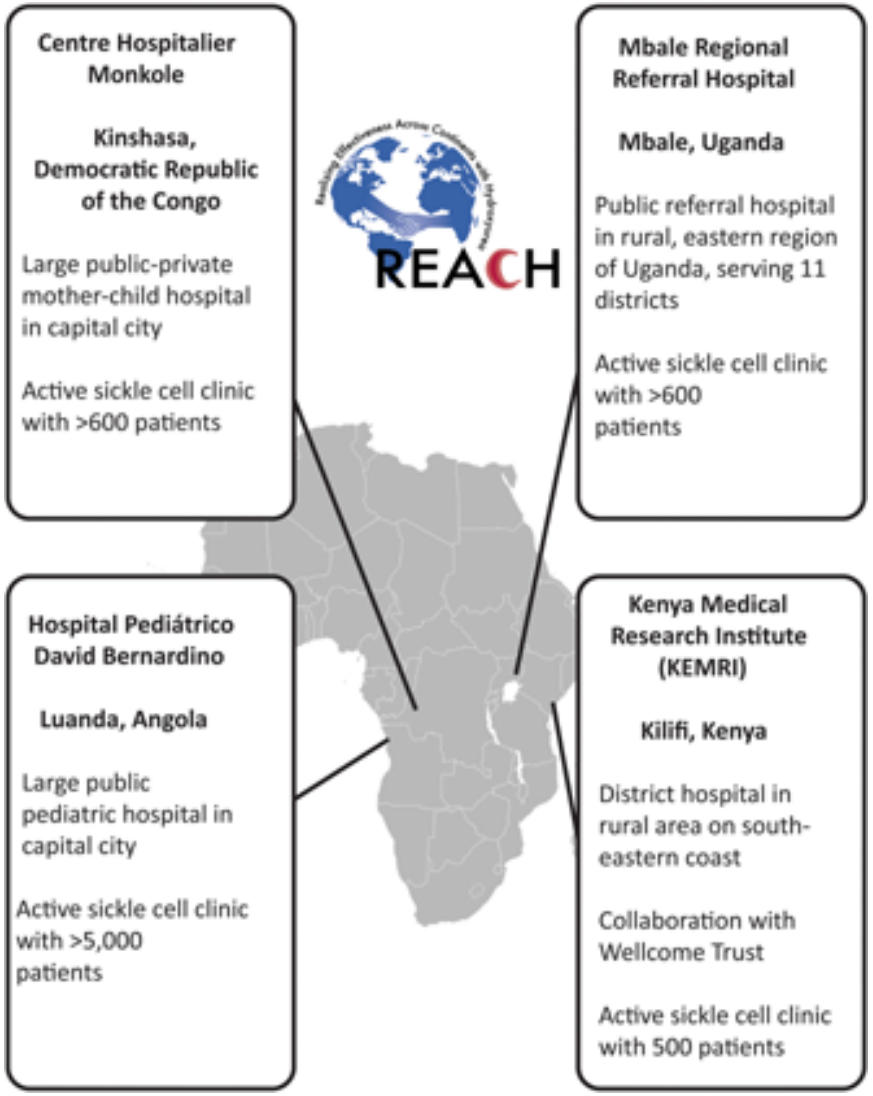
A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease

Elliott Vichinsky, M.D., Carolyn C. Hoppe, M.D., Kenneth I. Ataga, M.D., Russell E. Ware, M.D., Ph.D., Videlis Nduba, M.B., Ch.B., M.P.H., Amal El-Beshlawy, M.D., Hoda Hassab, M.D., Maureen M. Achebe, M.D., M.P.H., Salam Alkindi, M.B., B.Ch., R. Clark Brown, M.D., Ph.D., David L. Diuguid, M.D., Paul Telfer, M.D., Dimitris A. Tsitsikas, M.D., Ashraf Elghandour, M.D., Victor R. Gordeuk, M.D., Julie Kanter, M.D., Miguel R. Abboud, M.D., Joshua Lehrer-Graiwer, M.D., Margaret Tonda, Pharm.D., Allison Intondi, Ph.D., Barbara Tong, Ph.D., and Jo Howard, M.D., for the HOPE Trial Investigators*

What Did These Trials Have in Common?

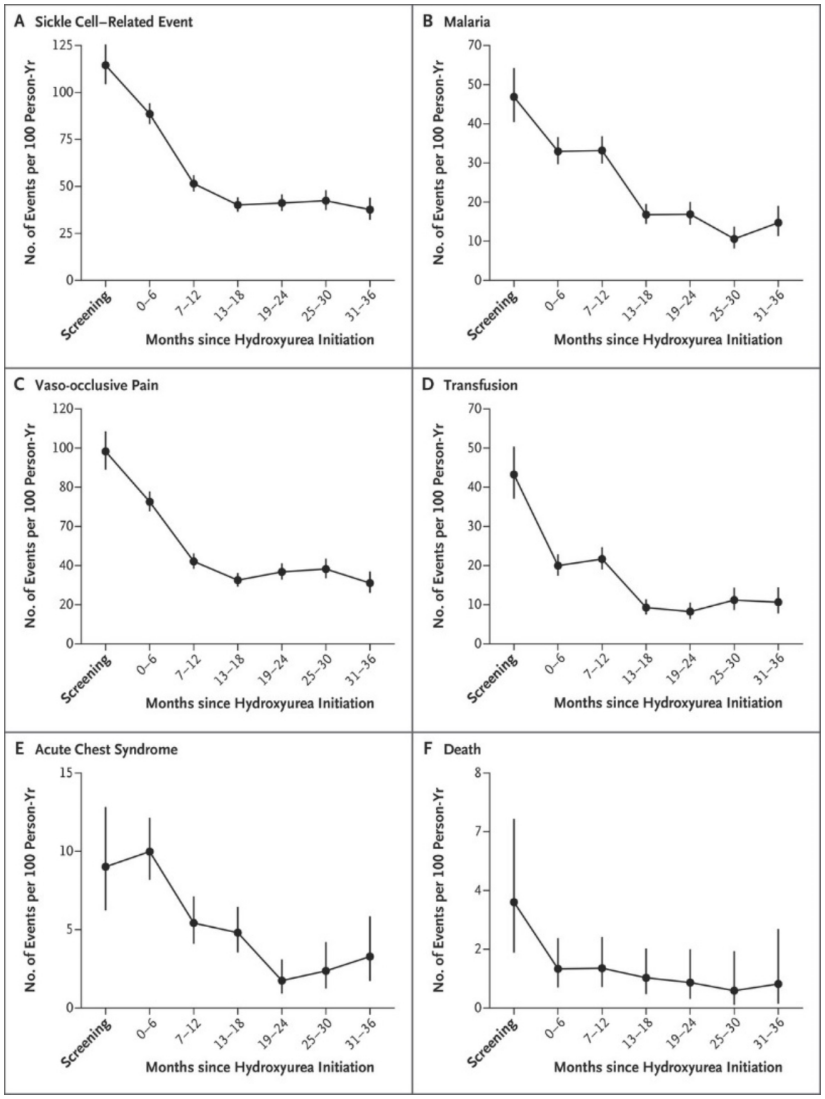
- Well designed and developed study and protocol
- Involvement of the steering committee composed of senior SCD investigators in study design and monitoring
- Involvement and extensive meetings with all institutional PIs

Hydroxyurea Therapy for Children With Sickle Cell Anemia in Sub-Saharan Africa: Rationale and Design of the REACH Trial



Pediatric Blood & Cancer
Volume 63, Issue 1, pages 98-104, 14 AUG 2015 DOI: 10.1002/pbc.25705
http://onlinelibrary.wiley.com/doi/10.1002/pbc.25705/full#pbc25705-fig-0001

Adverse events before and during Hydroxyurea treatment



Tshilolo L, et al. *N Engl J Med* 2019;380:121-31.

TRANSACTIONS OF THE AMERICAN CLINICAL AND CLIMATOLOGICAL ASSOCIATION, VOL. 127, 2016

PRIMARY STROKE PREVENTION IN CHILDREN WITH SICKLE CELL ANEMIA LIVING IN AFRICA: THE FALSE CHOICE BETWEEN PATIENT-ORIENTED RESEARCH AND HUMANITARIAN SERVICE

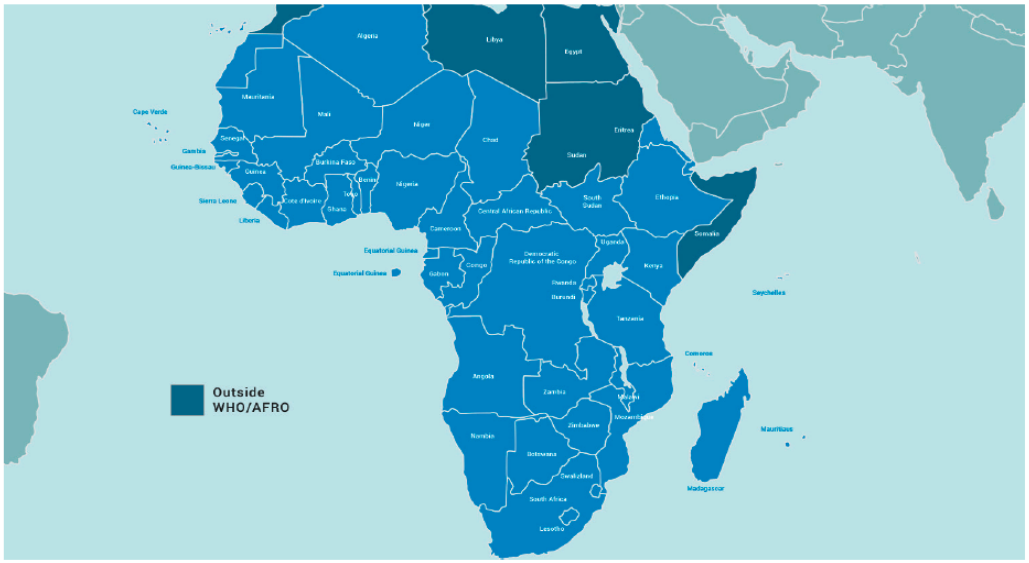
MICHAEL R. DEBAUN, MD, MPH, *and (by invitation)* NAJIBAH A. GALADANCI, MBBS, MPH, ADETOLA A. KASSIM, MBBS, LORI C. JORDAN, MD, PHD, SHARON PHILLIPS, MSPH, *and* MUKTAR H. ALIYU, MBBS, DrPH

We strongly believe that carefully crafted hypothesis-driven patient-oriented research in low-resource settings can be leveraged to advance the field, to build capacity, and to prevent human suffering.

1. **Opportunity:** A pharmaceutical company donation of study drug, hydroxyurea, did not translate into our academic institution to accept the donated product.
Solution: Initially purchased the study drug, hydroxyurea therapy from our institutional pharmacy, but ultimately had to find a pharmaceutical company that had readily available hydroxyurea in Nigeria. We also had to ensure that the Nigeria National Agency for Food and Drug Administration and Control (Nigeria equivalent to the United States Federal Drug Administration), approved the pharmaceutical company production of hydroxyurea therapy.
2. **Opportunity:** Donating and shipping large equipment to the study site. In this case, the shipping of imaging transcranial Doppler machines that weigh more than 400 pounds.
Solution: To the extent possible, limit the dependence of starting the trial on the study site receiving large equipment. We elected to use non-imaging transcranial Doppler ultrasound technology with machines that can be shipped easily via a postal carrier.
3. **Opportunity:** The dual level of legal oversight (both university counsel and outside counsel with expertise in the legal affairs of Nigeria) required initiating a trial in Nigeria.
Solution: To the best of our ability, anticipate potential legal and regulatory barriers for initiating the trial in Nigeria, such as seeking out approval from the Nigeria National Agency for Food and Drug Administration and Control and

4. **Opportunity:** Research team members travel from Nigeria to the United States, with limitations in obtaining a visa from Nigeria to the United States.
Solution: Apply for visas sufficiently in advance, up to 1 year before anticipated travel. Also, when hiring Nigeria-based research staff, the perceived ability to secure a visa for travel to the United States should be included in the screening process.
5. **Opportunity:** Ability to ensure that the hydroxyurea capsules that are available in Nigeria are of sufficient quality to be used in a clinical trial.
Solution: Identify a United States company that can determine the quality of the study drug (hydroxyurea) in an ongoing, reliable fashion.

Africa and MENA
Middle East Mediterranean and Africa



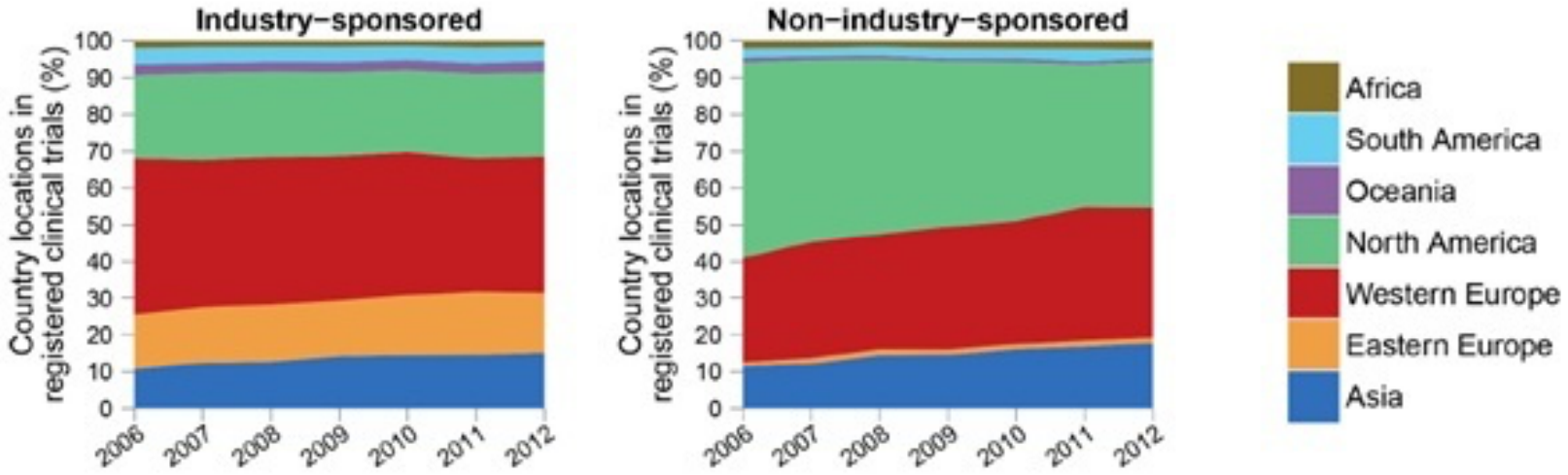
Zannad F, Sobhy M, Almahmeed W, et al. Clinical research in Africa And Middle East: roadmap for reform and harmonisation of the regulatory framework and sustainable capacity development. Journal of Global Health Reports. 2019;3:e2019082.

Clinical Research in Africa and the Middle East (MEMA)

- Region composed of 68 countries 20% of the worlds population
- Hosting only 6% of world wide registered clinical trials.
- Despite large pool of patients and a genetically diverse population.
- Hurdles to clinical trials are many.

Zannad F, Sobhy M, Almahmeed W, et al. Clinical research in Africa And Middle East: roadmap for reform and harmonisation of the regulatory framework and sustainable capacity development. Journal of Global Health Reports. 2019;3:e2019082.

Annual Distribution of Trial Location



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Clinical Research Regulation

- The Cardiovascular Clinical Trialists Middle East Mediterranean and Africa (CVCT-MEMA) 2019 White Paper Meeting in Cairo
- The contribution of the MEMA region to high standard health knowledge and actionable data is an important unmet need
- There are various clinical research centers, mostly affilated with academia that oversee and implement CT under licensed regulation by each country's ministry of health.
- Trials conducted according to local and international regulations and ICH-GCP (internacional council for harmonization of technical requirements for pharmaceuticals for human use).

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Hurdles to Clinical Trial Conduct

- Lack of national regulatory laws
- Lack of recognition for the need to develop sustained research infrastructure or institutional review mechanisms
- Lack of robust international standard regulatory frame work
- Uncertain public confidence
- Poor awareness of the importance of clinical research
- Paucity of clinical trials performed in the region with a low rate of publication (50%)
- Common non inclusion of local investigators in authorship reflecting lack of leadership role

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Medicines Regulation in Africa: Current State and Opportunities

Margareth Ndomondo-Sigonda1,2 • Jacqueline Miot1 • Shan Naidoo3 Alexander Dodoo4 • Eliangiringa Kaale5

Key Points

All African countries, except one, have National Medicines Regulatory Authorities

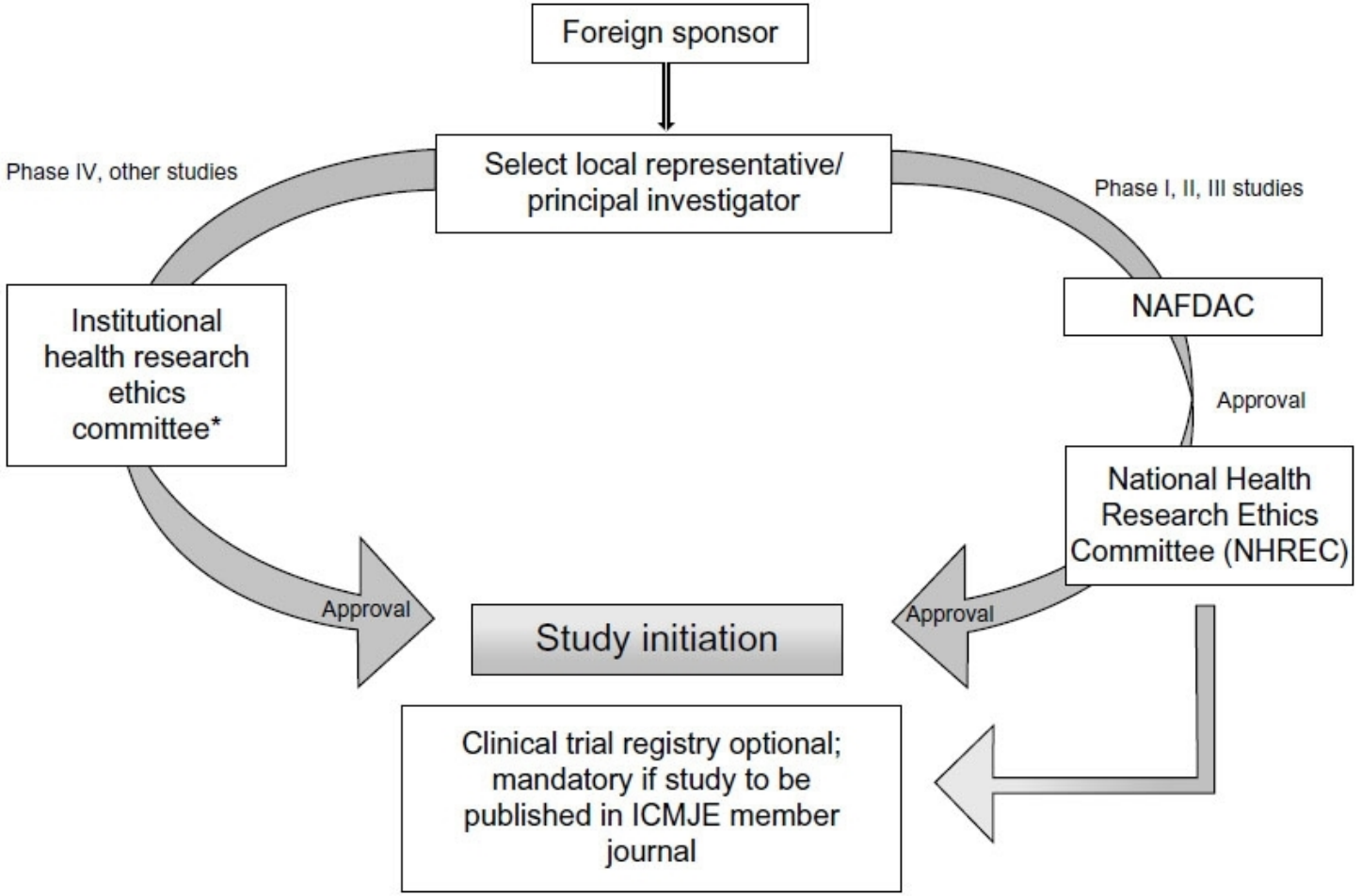
No national medicine regulatory authority in Africa can undertake the full range of regulatory functions

The proposed African Medicines Agency provides an opportunity for harmonizing and strengthening NMRAs in Africa

In the proposed agency document only one paragraph devoted to clinical research regulation

Pharm Med (2017) 31:383–397

Zannad F, Sobhy M, Almahmeed W, et al. Clinical research in Africa And Middle East: roadmap for reform and harmonisation of the regulatory framework and sustainable capacity development. Journal of Global Health Reports. 2019;3:e2019082.


Foreign sponsor
Select local representative/ principal investigator
Phase IV, other studies
Phase I, II, III studies
Institutional health research ethics committee*
NAFDAC
Approval
National Health Research Ethics Committee (NHREC)
Approval
Approval
Study initiation
Clinical trial registry optional; mandatory if study to be published in ICMJE member journal

Status in different countries

MEA Region Countries	Regulation in place	CT Guide	Healthy subjects	File Submission	Competent Authorities§	Procedure	Site	IP Importation	Study Report	Fees	SAE Reporting	Document archival	Approval Timelines	Insurance for CT	IP temporary use	Biological samples export
Algeria	YES*	YES	YES	Paper	Local	Sequential	Public	CCA	annual	NO	ICH regulation	15 years	90 working days	YES	Information Not Available	Information Not Available
Burkina Faso	YES†	NO	YES	Paper	Central	Information Not Available	Both	Information Not Available	annual	YES	ICH regulation	Information Not Available	90 working days	YES	Information Not Available	YES
Cameroun	Information Not Available	NO	Information Not Available	Paper	Information Not Available	Information Not Available	Public	Information Not Available	Information Not Available	Information Not Available	ICH regulation	Information Not Available	Information Not Available	Information Not Available	Information Not Available	YES
Ivory Coast	Information Not Available	NO	Information Not Available	Paper	Central	Sequential	Information Not Available	Information Not Available	Information Not Available	YES	ICH regulation	ICH regulation	90 working days	YES	YES	Information Not Available
Egypt	YES†	YES	YES	Electronic + Paper	Local	Sequential	Public	IL	Bi-annual	YES	ICH regulation	ICH regulation	90 working days	YES	YES	YES
Iran	YES*	NO	YES	Electronic + Paper	Central	Sequential	Information Not Available	Information Not Available	Bi-annual	NO	ICH regulation	ICH regulation	Information Not Available	Information Not Available	Information Not Available	Information Not Available
Jordan	YES‡	YES	YES	Electronic + Paper	Local	Sequential	Both	IL	annual	YES	ICH regulation	ICH regulation	90 working days	YES	Information Not Available	YES
Kenya	YES*	NO	YES	Electronic + Paper	Central	Parallel	Both	CCA	annual	NO	ICH regulation	ICH regulation	90 working days	YES	Information Not Available	Information Not Available
Lebanon	YES*	NO	YES	PS	Local	Sequential	Both	IL	annual	NO	ICH regulation	ICH regulation	90 working days	YES	Information Not Available	YES
Morrocco	YES*	YES	YES	PS	Central	Sequential	Both	IL	Bi-annual	NO	ICH regulation	20 years	More than 90 working days	YES	Information Not Available	YES
Nigeria	Information Not Available	NO	Information Not Available	PS	Local	Parallel	Public	CCA	annual	YES	ICH regulation	ICH regulation	90 working days	YES	Information Not Available	YES
Pakistan	YES‡	NO	YES	Electronic + Paper	Central	Sequential	Both	IL	annual	NO	ICH regulation	Information Not Available	More than 90 working days	YES	Information Not Available	Information Not Available
Congo	YES*	NO	YES	Paper	N/A	Information Not Available	Information Not Available	Information Not Available	Information Not Available	Information Not Available	ICH regulation	Information Not Available	Information Not Available	Information Not Available	Information Not Available	Information Not Available
Saudi Arabia	YES‡	YES	YES	Electronic	Central	Parallel	Both	ICH	annual	YES	ICH regulation	ICH regulation	90 working days	YES	NO	YES
South Africa	YES‡	YES	YES	Electronic + Paper	Local	Parallel	Both	CCA	annual	YES	ICH regulation	15 years	More than 90 working days	YES	Information Not Available	YES
Tunisia	YES†	NO	YES	Electronic + Paper	Central	Parallel	Both	CCA	annual	NO	ICH regulation	ICH regulation	90 working days	YES	Information Not Available	YES

CVCT-MEMA Areas of Unmet needs

- Reforming the regulatory framework
- Capacity Building
  - Objective 5 of WHO global action plan for prevention and control on NCD
  - Developing a cadre of trained local investigators and health care professionals with CT expertise
  - Locally operating CROs ideally within the setting, and being led by academic professionals
- Moving to digital health
- Funding for clinical trials

Towards an international standards clinical trial regulatory framework Recommendations from the Regulatory Summit at CVCT MEMA 2018.

1-Deleting the redundancy and overlap in approval procedures of clinical trials in preclinical requirements of the investigational products.

2-Defining in a clear manner the maximum timeline expected to obtain approval from the competent authorities before initiating a trial.

3- Defining a process for streamlining approvals for investigational medical product stock import for the logistical convenience of the trial initiation.

4-Enhancing the clarity regarding the procedures of bioequivalence studies.

5-Setting rules for membership, accreditation, training, functioning, capacity of reviewing protocol and monitoring studies of clinical trials review boards. (Silverman et al., 2015) Clarifying the objectives and respective duties of national ethics boards, local ethics committees and institutional review boards. Defining an authority hierarchy. Ideally avoiding multiplicity/redundancy of such research ethics committees.

6- Defining simplified approval procedures for non-interventional (observational) studies.

7- Issuing a detailed pharmacovigilance guideline, consistent with the current international requirements, including homogenous timeline for reporting serious adverse events (SAEs), conditions of waiver of reporting protocol specified or study endpoints SAEs, conditions of reporting causality. (Cheaib 2016)

8- Clarifying the need and process, if any, of certification of clinical trial sites.

9- Clarifying procedures governing informed consent, including the need of translation of consent forms, and managing transparent information and consent for illiterate (Baiden et al., 2016) and vulnerable participants.

10- Setting a legal framework for biobanking and material transfer agreements, including across national borders.

11- In the context of genomics and biobanking research (Sathar and Dhai 2012), setting guidelines and governance frameworks of sample and data sharing, including de-identification processes, securing data protection, appropriateness of using broad consent and sample access for secondary use, feedback of individual genetic findings. Clarifying the justification of, and optimally waiving the prohibition of bio-specimen export, which impedes the principles of openness, storage, sharing and secondary use of biosamples. (de Vries 2017; Heeney and Kerr 2017; Barchi and Little 2016; Mahomed et al. 2016)

12-Revising the “criminal penalty” (Kamalo et al. 2016) regulation (“no-fault compensation for research-related injuries”). Assessing the occurrence of unexpected serious adverse events only in the light of its relatedness to the investigational product rather than the already pre-existing condition, and enacting a regulatory requirement for insurance-based compensation for biomedical research-related injuries.

13- Setting a legal framework and mechanisms for sponsors to provide long-term post-trial access to trials treatments proven beneficial

14- Update subject privacy and data confidentiality legislation consistently with international standards.

15- Seek harmonization of technical requirements and guidelines for clinical trials across Middle East, Mediterranean and African countries.

Summit For Operational Strategies for Oncology Clinical Trials in Africa

TABLE 1. List of Participating Experts and Countries at the 1st All Africa Clinical Trial Summit and the Operational Strategy for Clinical Trials in Nigeria Summit

Participating Experts	Countries Represented
1st All Africa Clinical Trial Summit (June 2017, Lagos, Nigeria)	Benin, Cameroon, Ghana, Nigeria, United States
Biopharmaceutical company representatives	
African state and federal health officials	
Health care leaders	
African national regulatory agency representatives	
Professors of pharmacy and radiology	
Operational Strategy for Clinical Trials in Nigeria Summit (April 2018, Vienna, Austria)	
Professors of pharmacy, radiology, and mathematical computing	Nigeria, South Africa, United Kingdom, United States
Medical doctors	
Pharmacists	
Biopharmaceutical company representatives	
Heads of procurement and data acquisition	
Blockchain business founders	
Clinical operations, quality, and oversight experts	
Patient recruitment and retention executives	
Management consultant	

Operational Strategies for Clinical Trials in Africa
Katy M. Graef, PhD1; Ifeoma Okoye, MBBS2,3; Naomi O. Ohene Oti, MPH, MGCNM(ONC)4; Jennifer Dent, MBA1; and Folakemi T. Odedina, PhD5,6JCO Global Oncol 2020 6:973-981

Oncology Trials

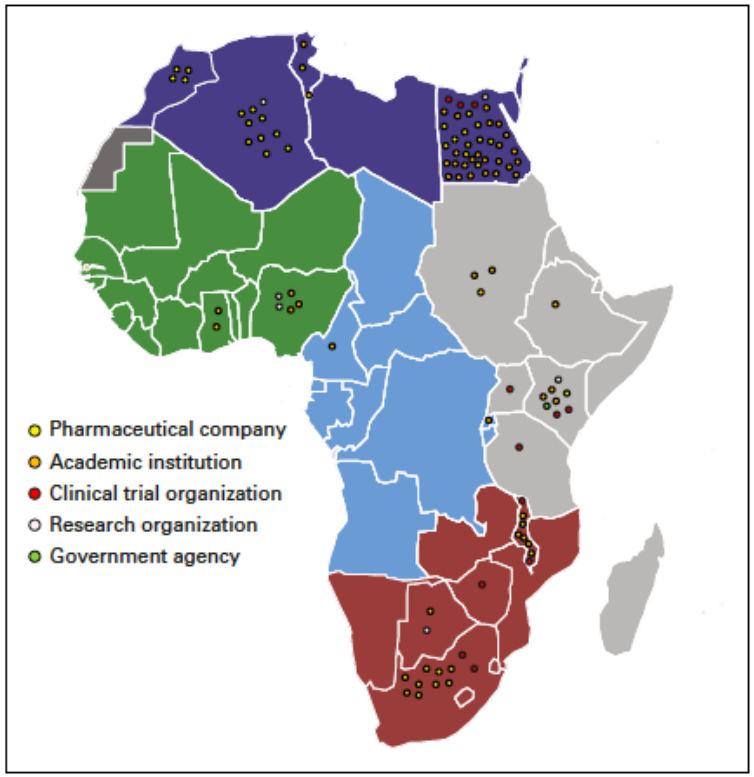


FIG 1. Map of ongoing cancer clinical trials in Africa. Circles represent individual clinical trials, with the color of the circles denoting the study's primary sponsor type.

Operational Strategies for Clinical Trials in Africa
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FIG 2 Map of African countries with medicines review agencies that have clinical trial oversight authority. Review agencies that have clinical trial oversight authority are noted in dark gray. Although not shown on the map, the Cabo Verde's medicines review agency has clinical trial oversight authority. Records demonstrating the clinical trial oversight authority of the medicines review agencies of the countries shown in light gray are unavailable.

Recommendations

TABLE 2. Recommendations From the 1st All Africa Clinical Trial Summit and the Operational Strategy for Clinical Trials in Nigeria Summit

Category	Recommendation
Funding	Increase funding for clinical trials
Regulation	Improve transparent clinical trial regulatory infrastructure and ensure consistent enforcement
Capacity building	Encourage international pharmaceutical companies to host clinical trials (investigational and postmarket) in Africa, with the goal of ensuring cancer drugs are safe and efficacious in African ethnicities
	Build clinical trial capacity
	Curate a database of African sites capable of conducting clinical trials that meet international standards
Africa-centric approach	Encourage clinical trials on local innovations, including traditional medicines, and for Africa-specific health issues
	Create an Africa-wide clinical trial network to support collaboration and create a continent-wide strategy
	Leverage technology to improve clinical trial efficiency and effectiveness
Patient engagement	Improve patient education, awareness, and engagement
	Promote patient recruitment and retention models

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Regulation of biomedical research in Africa

- Current guidelines for international research are undermined by exceptions that favour some researchers and sponsors in the developed world
- Reliance on international legislation and guidelines does not adequately protect research participants in Africa
- Local and regional regulatory frameworks and legislation are needed to interpret international guidelines in the light of local socio-political realities
- New laws could focus on informed consent procedures, local research ethics committees, standards of care, and distributive justice (for example, compensation and post-trial benefits)

Chima SC BMJ 2006 Apr 8; 332(7545): 848–851

How Africa could become a new center for clinical trials

***Sponsored Content by Cerba Research* Jul 22, 2021**

- The virtual absence of Africa from the clinical trials map presents a significant problem. As the continent presents an enormous amount of genetic diversity, if it is not well represented in clinical trials, the trial findings cannot be universal to large populations.
- Genetic analyses have clearly shown that ethnic groups show variable results to different treatments, so it is vital to carry out clinical trials in Africa, as Africa endures diseases linked to poverty more than any other continent, and the interventions typically used to treat or cure the diseases of which Africans suffer are developed elsewhere.
- Cerba Research firmly believes that Africa provides a significant opportunity for pharmaceutical and biotech companies, as well as nongovernmental organizations seeking out low-cost study sites, low risk of litigation and a diverse participant population.
- The latter makes Africa a prime location for research, as the diseases of affluence and poverty are widespread. Moreover, most of the potential patients for enrollment in clinical trials have not received any previous treatment for their diseases – either because they cannot afford it, or it is not available – meaning patient recruitment is easier.

Current situation: industry sponsored trials

- Many studies being proposed: competition for study subjects.1 day delay in bringing drug to market leads to a loss of US$ 1,300,000 in unrealized sales
- Study conduct delegated to CRO, often a way to circumvent regulation including HIPPA
- Little contact of institutional PI with steering committee
- Focus on patient enrollment and incentives to PIs
- Questions on cost of new therapies after approval

Branes Mark and Wallace Nick Law and Ethics Affecting Clinical trials in Africa Journa of Health Care Law and Policy 2017 19 246

What Laws Apply

- Local regulations when existing may be poorly enforced
- South Africa, has adopted detailed legal requrements for protection of human research subjects and data privacy. Other countries having regulation include Egypt, Tunisia, Saudi Arabia and Lebanon
- As of 2017 OHRP: only 25 African Countries with laws governing general human subject research, research injury, CT registries, genetics, cloning
- Some have suggested that absence of regulation is purposeful to attract the benefits of clinical research

Branes Mark and Wallace Nick Law and Ethics Affecting Clinical trials in Africa Journa of Health Care Law and Policy 2017 19 246

From: The state of health research governance in Africa: what do we know and how can we improve?

Have research laws and legislation	Laws and legislation in draft form	Lack of research laws and legislation
Kenya, Gambia, Malawi, Mali, Mauritius, Rwanda, United Republic of Tanzania, Uganda, Zambia, Zimbabwe, Nigeria, Cameroon, Gabon, Congo, Benin, Senegal, Ghana, Mozambique (18)	Lesotho, Liberia, Sierra Leone, Swaziland, Niger (5)	Ethiopia, Botswana, Namibia, Seychelles, South Sudan, Guinea-Bissau, Côte d'Ivoire, Burundi, Mauritania, Democratic Republic of the Congo, Cape Verde, Eritrea (12)

Nabyonga-Orem et al. Health Res Policy Sys (2021) 19:11

U.S. Laws That Apply Extraterritorially

- Federal Policy for the protection of human subjects consits of 4 parts part A known as Common Rule applies to NIH and CDC funded studies
- FDA regulations apply if trials are designed to have data submitted to the FDA for marketing approval
- Privacy and confidentiality regulations
- Foreign corrupt practices act: May cover even authorship

Branes Mark and Wallace Nick Law and Ethics Affecting Clinical trials in Africa Journa of Health Care Law and Policy 2017 19 246

International Ethical Guidelines for Health Related Research Involving Humans

- First relased in 1982 updated in 2016 by the Council of International Organizations of Medical Sciences
- Designed so that people in low income settings receive equitable benefits from their partipation in medical research.
- Problem issues remain
  - Informed consent: How informed? how easily understood?
  - Avoiding undue inducements when subjects lack medical alternatives
  - Ethical issues identifying subjects: structural coercion

Branes Mark and Wallace Nick Law and Ethics Affecting Clinical trials in Africa Journa of Health Care Law and Policy 2017 19 246

Perceived benefits and risks of participation in a clinical trial for Ugandan children with sickle cell anemia

Aubri S. Carman, Casey Sautter, Juliana N. Anyanwu, Andrew S. Ssemata, Robert O. Opoka, Russell E. Ware, Joseph Rujumba, Chandy C. John

First published: 28 May 2019 | https://doi-org.ezproxy.aub.edu.lb/10.1002/pbc.27830 | Citations: 2

Our study findings highlight the generally poor state of health of Ugandan children with SCA, the desperation by caregivers for anything that could improve the child's health, and the inevitable improvements in care that result from strict adherence to a study protocol, even a protocol based on local guidelines. Studies in this vulnerable population must be careful not to portray improved care as a primary incentive for participation.

Phase 3 Oncology Clinical Trials in South Africa: Experimentation or Therapeutic Misconception?

Journal of Empirical Research on Human Research Ethics
2016, Vol. 11(1) 47–56

DOI: 10.1177/1556264616637736
jre.sagepub.com
SAGE

Tina Malan[1] and Keymanthri Moodley[1]

Abstract

Although clinical research in oncology is vital to improve current understanding of cancer and to validate new treatment options, voluntary informed consent is a critical component. Oncology research participants are a particularly vulnerable population; hence, therapeutic misconception often leads to ethical and legal challenges. We conducted a qualitative study administering semi-structured questionnaires on 29 adult, Phase 3, oncology clinical trial participants at three different private oncology clinical trial sites in South Africa. A descriptive content analysis was performed to identify perceptions of these participants regarding Phase 3 clinical trials. We found that most participants provided consent to be included in the trial for self-benefit. More than half of the participants had a poor understanding of Phase 3 clinical trials, and almost half the participants believed the clinical trial did not pose any significant risk to them. The word "hope" was used frequently by participants, displaying clear optimism with regard to the clinical trial and its outcome. This indicated that therapeutic misconception does occur in the South African oncology research setting and has the potential to lead to underestimation of the risks of a Phase 3 clinical trial. Emphasizing the experimental nature of a clinical trial during the consent process is critical to address therapeutic misconception in oncology research.

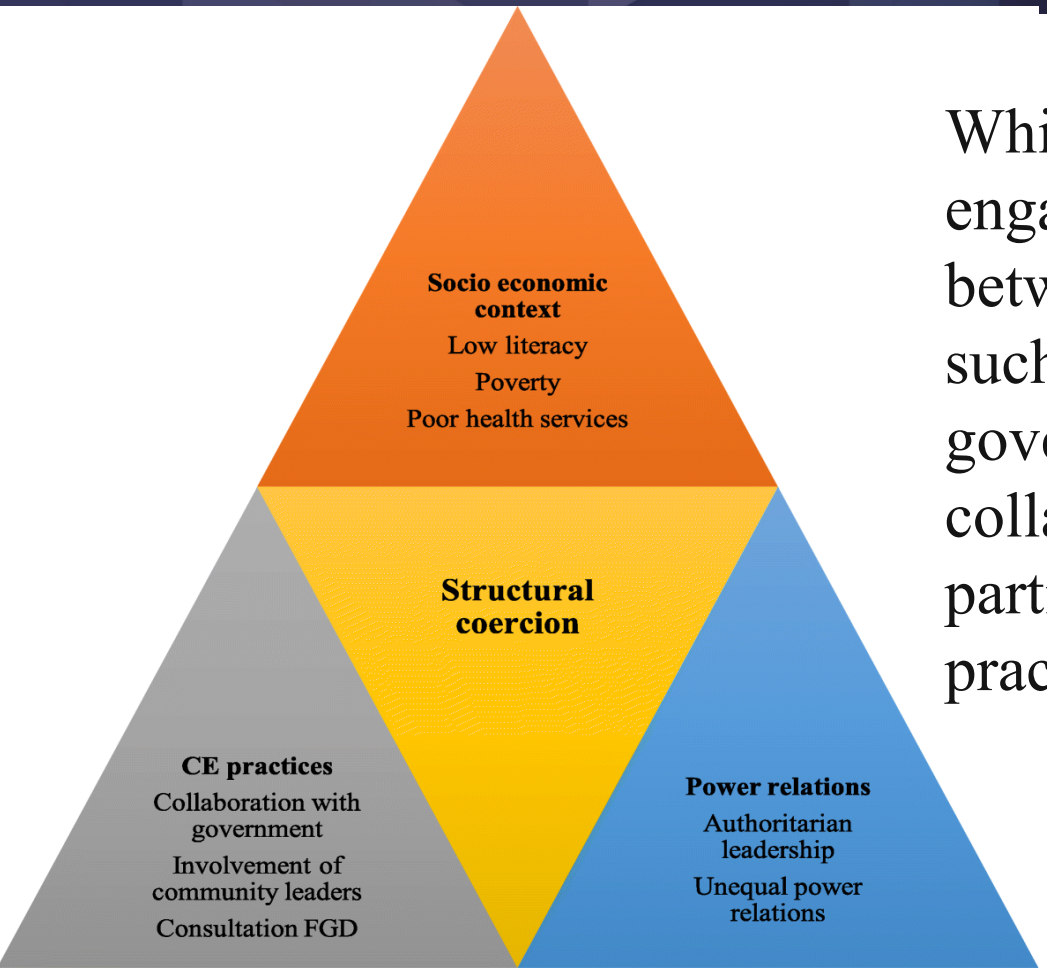
Results

- Most participants provided consent to be included in the trial for self benefit
- More than half the patients had a poor understanding of phase 3 clinical trials and 50% thought that trials did not pose any risk to them
- Therapeutic misconception

Structural coercion in the context of community engagement in global health research conducted in a low resource setting in Africa

Urban case study	Rural case study	Hospital case study	
Study design	Observational study	Cluster Randomised Trial	Longitudinal cohort study
Setting	Urban setting	Rural setting	Hospital setting
Target population	School communities School children	Villages All households in selected villages	TB patients
CE activities	Meetings with Primary Education Advisors Meetings with Parents and Teacher Association committees Meetings with parents Meetings with students Study information sent to communities	Community involvement to select volunteers and committees Training of community volunteers Village workshops facilitated by community volunteers Community volunteers involved in monitoring and evaluation	Consultation FGD Sensitization of health care workers
Aims of CE	Raise awareness about the study To get feedback on the research and engage in two-way dialogue with communities	To educate and empower communities to implement interventions aimed at preventing malaria	To explore patients and community members' understanding of study information and to seek their feedback

Structural coercion created through the interplay of key themes



While guidelines on community engagement promote collaborations between researchers and stakeholders such as government agencies and non-governmental actors[6], such collaborations may influence research participation and undermine ethical practice.

Nyirenda et al. BMC Medical Ethics (2020) 21:90

Conclusions

- Countries in the MEMA region are underepresented in the global clinical trial arena. Efforts at capacity building and training of specialists are needed.
- Regional and international collboration could greatly enhance national efforts
- Several proposals have been made to improve participation and access to clinical trials in cardiovascular disease and oncology. What about SCD?
- Significant issues of regulation remain unsolved and a clear regulatory framework(s) needs to be developed
- Training is needed to ensure better compliance with existing guidelines for informed consent, privacy and patient recruitment

Take home message

Clinical trials should be conducted only if the researcher knows that they are the right person for the task, that the question is worth addressing, and that the study will provide a valid answer. Ethics should not be viewed as risk management.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