Article title: Meeting Report: South African Medical Research Council Standard of Care in Clinical Research in Low- And Middle-Income Settings Summit, November 2017
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Meeting Report: **South African Medical Research Council Standard of Care in Clinical Research in Low- And Middle-Income Settings Summit, November 2017**

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Running Head: Standard of care for HIV clinical trials summit

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Abstract

Introduction: The South African Medical Research Council (SAMRC) convened a summit to discuss issues relating to standard of care (SoC) in HIV prevention clinical trials, both for treatment and prevention of disease. Policymakers, regulators, ethicists, experts in the law (as it pertains to medical research), researchers, representatives of advocacy groups, and the HIV Vaccine Trials Network (HVTN) presented a framework within which SoC principles could be articulated.

Discussion: Summit participants discussed how and when to include new modalities of HIV treatment and prevention into existing clinical practice guidelines, and by extension in clinical trial protocols. Participants involved in the execution of care and the scale-up of new interventions, in particular, the roll out of pre-exposure prophylaxis (PrEP), presented the opportunities for and challenges to scaling up interventions, and their experience with demonstration projects of PrEP. Advocates and community members propagated the need to make interventions that could avert HIV infection available as soon as possible. Experts in evidence-based guideline development discussed the nuances in evaluating evidence for policy and the mechanisms for getting medicines on the Essential Medicines List in South Africa. Given the variability in clinical trial efficacy of PrEP amongst different populations, scientists and statisticians discussed the various biological, virological and immunological reasons for this heterogeneity.

Conclusions: Input was given as to the impact of introducing PrEP in other HIV prevention trials, and the considerations for the design of both antiretroviral (ARV)-based and non-ARV based HIV prevention trials. The meeting recommended supporting access to PrEP in HIV prevention trials by 1) developing PrEP access plans for HIV vaccine trials; 2) creating a PrEP fund that would supply PrEP to sites conducting HIV prevention trials via a central procurement mechanism; and 3) support the safety monitoring of PrEP.

Introduction

The South African Medical Research Council (SAMRC) has a mandate to address issues that could potentially impact the conduct of health research. In 2017, the SAMRC convened a summit in Cape Town to address the standard of care (SoC) in HIV prevention clinical trials in lower- and middle-income countries (LMIC) such as South Africa. The overall objective of the meeting was to engage regulatory, legal and ethical frameworks, whilst considering perspectives of government, community organisations and advocates, and the funders of research, to review the principles behind setting SoC for clinical trials of both treatment and prevention in LMIC.

HIV prevention has evolved over the last decade. In 2015, the World Health Organization (WHO) made a recommendation for the inclusion of oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC, brand name Truvada) pre-exposure prophylaxis (PrEP) as part of a combination HIV prevention package that should be targeted at people at substantial risk of HIV infection [1]. TDF/FTC had been licensed at the time of the summit, in 17 countries for use as PrEP and was included in the WHO Essential Medicines List (EML). At the time of the summit, although PrEP was approved in South Africa, its availability was limited to National Department of Health (NDoH)-sanctioned sub-populations (specifically men who have sex with men [MSM] and sex workers) and research-led demonstration projects.

Heterosexual women are at high risk of HIV acquisition and thus make up a large proportion of participants in HIV prevention clinical trials conducted in South Africa. This led to the HIV Vaccine Trials Network (HVTN) co-leading the summit with the SAMRC. Here we summarise the viewpoints and discussions that took place at the summit in November 2017.

Discussion

Regulatory consideration for SoC in treatment and prevention

A modern definition of SoC is 'that which a minimally competent physician in the same field would do under similar circumstances' [2]. SoC should be established prior to enrolment in a clinical trial. In the context of HIV prevention clinical trials, SoC usually includes a basic prevention package of sexual health counselling; every participant has access to this care regardless of whether they are in a placebo/control arm or receiving treatment. Regulatory requirements for clinical trials fall into three categories: 1) legislative, including Section 21 and 19 of the Medicines and Related Substances Act and General Regulations [3]; 2) standard, including the Nuremberg Code, Declaration of Helsinki and the Belmont Report; and 3) guidance, including guidelines from the WHO and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) on Good Clinical Practice (GCP), local ethics, and the National Health Research Ethics Council. GCP compliance provides public assurance of a participant's rights, safety and wellbeing. GCP requires the SoC to include informed consent, duty to warn of adverse outcomes, the potential for post-trial provision of treatment, and adverse drug event reporting.

Integrated thinking about SoC

The meaning of SoC depends on the context. For instance, SoC can be defined as 1) an established, effective intervention; 2) the level at which the average prudent provider would

practice; 3) the level of care that ought to be delivered under appropriate conditions; or 4) care considered proper and best practice. In an idealized world, if something is ethical in one context then it is ethical in every context. In reality, not every treatment approach is standardized throughout the world. The purpose of a SoC is to promote consistency and ensure equity in the system, for treatment or research.

Several questions are inherent when discussing SoC. *How are standards established?* In an objective and ideal system, it is through an accumulation of evidence-based knowledge over time. *Who decides what the standards are?* It is important that those involved be as impartial as possible. *How 'standard' is the standard going to be?* This takes into account high-level and big-picture considerations like affordability and political issues. *Is the standard universal?* Apart from a universal standard, there is an international consensus view, which is a pragmatic view comprised of three conditions: 1) valid science that is credible, feasible, and appropriate; 2) social value; and 3) the individual risk or harm must be less than the likelihood of benefit [4].

Current Standard Treatment Guidelines (STG) as the minimum SoC

It is accepted that the current standard treatment should be available in the control arm of a randomised controlled trial (RCT) evaluating a new treatment intervention. For prevention studies of disease, especially HIV prevention research, participants in the control arm of a clinical trial should not be disadvantaged or at greater risk of acquiring HIV than if they had received the current locally available standard of prevention. However, in HIV vaccine research, there is not yet evidence that the intervention arm will be effective, thus necessitating interventions that augment prevention modalities in both arms of a study.

In South Africa, the NDoH is the custodian of quality to promote sustainable access to and availability of medicines in the public sector. There are four basic criteria for deciding whether a medicine ought to appear on the Essential Medicines List (EML): 1) public health need; 2) safety, efficacy and quality; 3) pharma-economics/cost; and 4) practice considerations.

Factors to be considered in implementing SoC in South Africa – the case study of prevention of mother-to-child transmission (PMTCT)

In 2013, UNAIDS developed a new SoC for PMTCT of HIV called Option B+ to replace the previously used Options A and B, which involved different regimens of antiretroviral therapy (ART)[5]. There was a large local debate after the international community proposed that South Africa implement Option B+, when the country was doing reasonably well with Options A/B. As it turned out, it was the right decision to move to Option B+; South Africa lowered the MTCT rate from 8% in 2009 to 2% in 2015 [6]. The key questions raised by this example were: how are decisions made globally, and what effect do outside bodies have on local/national SoC guidelines in South Africa? In this 2013 example, local researchers used local data for making decisions based on international guidance.

Ethics and law considerations for SoC

In the context of law, the term 'duty of care,' not SoC, is used. Duty of care is what courts use to determine whether or not somebody should be held negligent. In law, a health care professional is not expected to demonstrate the *highest* possible degree of professional skill. The courts have explicitly said they are just expected to exercise a *reasonable* degree of care and skill. Therefore, by law, the SoC has to be reasonable and is defined legally as conduct of minimal competency

that would be performed by someone in a similar circumstance [2]. Human rights take a slightly different, but similar, standard. The South African Bill of Rights discusses the right to health in Section 27 of the Constitution: 'The state has to take reasonable legislative measures within its available resources.' Therefore, any measures that don't meet the needs of the most vulnerable would be deemed unreasonable.

There were parallels between the debate on PrEP during the summit and the 2002 Treatment Action Campaign (TAC) nevirapine case [7]. In 2002, the South African health minister was opposed to any form of ARV nevirapine rollout. Therefore, the NDoH declared it would test feasibility at 18 test sites as a pilot study. The court was not convinced the government had to confine the rollout to only 18 test sites and held that the government's policy was unreasonable in that it did not allow for nevirapine administration elsewhere in the public health system where there was capacity and its use was medically indicated [8, 9]. While there are numerous differences between nevirapine treatment for new-borns and PrEP for a sexually transmitted infection, some issues remain pertinent in the context of adult PrEP. The court ruling did not mean that *everybody* could immediately claim access, but that the government should try to make access possible as soon as reasonable.

Evidence and guideline development

Guidelines are statements that include recommendations intended to optimize patient care that are informed by systematic reviews of evidence and assessment of the benefits and harms of alternative care options [10]. There has been a change in how guidelines are defined: increasingly, the field has recognized the need for systematic methods and transparency to inform how recommendations are developed [11]. In the field of HIV prevention and treatment, there are several guidelines available from the WHO, US Centers for Disease Control and Prevention (CDC), South African NDoH, and the South African HIV Clinicians Society. The decision around a recommendation, even if the evidence is strongly in favour of an intervention, should always consider other aspects such as cost, the balance between desirable and undesirable effects, and acceptability to those who will receive treatment.

The SAMRC has funded the South African Guidelines Excellence (SAGE) project, which is a multi-partner, 5-goal project to develop and implement primary care guidelines in South Africa [12]. Common problems SAGE aims to address include fragmentation between government programs or between the public and private sector, silos of activity, inefficiency, duplication, and potential conflicts in recommendations. Evidence is the primary building block for guideline recommendations and the challenge of a lack of agreed standards remains, which impacts the credibility of South African guidelines.

SoC considerations in LMIC

South Africa is one of the most unequal societies in the world, with a Gini coefficient of 0.63 [13]. Many clinical trial participants come from less privileged parts of South Africa and are regarded as vulnerable participants. The South African population is ~56 million, and an estimated 7.7 million people were HIV positive as of 2017 [14]. The GDP is around 5.4 trillion rand (US$350 billion), of which approximately 8.2% was spent on health in 2015 [15]. Although this exceeds the WHO recommendation of 5%, major challenges remain in the public health system.

One argument for why PrEP might not be provided consistently across all trial sites is that there is limited evidence for efficacy in South African heterosexual women. The question that ethics committees sit with is how to deliberate around SoC and prevention when there may not be consensus in the scientific community. The WHO recommends that tenofovir-based PrEP be offered to individuals at substantial risk for HIV infection as part of a comprehensive HIV prevention package. Based on a systematic review of 18 RCT of oral PrEP across a range of populations and settings, it was found that tenofovir-based oral PrEP was effective in reducing HIV infection risk across gender, PrEP regimen, dosing, and mode of acquisition [16].

In 2005, Solly Benatar, a prominent South African ethicist, encouraged researchers with his words: 'Contributing to sustainable improvements in health by progressively ratcheting the SoC upwards for research participants and their communities is an ethical obligation of those resource-rich countries who sponsor and implement research in poorer ones' [17]. This problem is prominent, and different agencies need to think creatively about how to collaborate, form partnerships, and together ensure some level of SoC provision. In 2016, the ethicist Jeremy Sugarman referred to what is now highly quoted as the 'rebuttable presumption' [18]. According to Sugarman, the onus is now on researchers to justify *not* offering PrEP to participants in HIV prevention trials.

Efficacy data on PrEP in women

Five RCT of oral PrEP that enrolled heterosexual women have demonstrated inconsistent efficacy in this population. Numerous confounders were suggested as possible factors, including biological (e.g., viral clade, vaginal environment) and behavioural (e.g., drug adherence, relationship status). A meta-analysis of these trials showed that drug adherence correlated with efficacy [19]. WHO guidelines recommend PrEP use for all populations at substantial risk of HIV, including young women in southern Africa. Further data are required to refine the estimates of PrEP efficacy in southern African women to aid in appropriate messaging and assessing the impact of PrEP on a population level [19].

The WHO guidance on PrEP were released in September 2015. By November 2015, Truvada was registered for its preventive indication, and the recently completed South African AIDS Committee guidelines also include the provision of PrEP taken daily for high-risk populations [20].

History of PrEP delivery in South Africa

In October 2015, the NDoH met to consider the soon-to-be-released WHO guidelines recommending universal or immediate treatment after HIV testing as well as PrEP. At that meeting, the National PrEP Technical Working Group was formed, which has been an important vehicle for guiding PrEP introduction into South Africa. Shortly thereafter, the Medicines Control Council licensed TDF/FTC for PrEP use and, by June 2016, the beginnings of a publicly-funded program began where PrEP was provided to sex workers as part of the National Sex Worker Program. It was one of the first nationally-funded PrEP programs in Africa and was lauded by UNAIDS [21]. Since then, the program has expanded to include sites for MSM, adolescent girls and young women.

Between 2016 and 2017, publicly-funded programs provided nearly 3,000 PrEP initiations at 17 sites across South Africa. A key take-home from the National Sex Worker Program data is that initially uptake was quite low, partly because prior to licensure, sex workers were sceptical as to the motives of including them in a program. But with increasing awareness of PrEP and perhaps expansion of access to other populations, there was a sense that use would increase. Other reasons for non-uptake are currently being explored in an operations research project. Since PrEP became available, there has been greater uptake in MSM populations than in the sex worker programs.

Challenges and successes of demonstration projects in South Africa

The National PrEP Technical Working Group has begun implementing demonstration projects for adolescent girls and young women. Those projects have evaluated a number of strategies including: creating materials that are sex-positive and targeted at young people; considering fixed facilities and mobile delivery models; drug-level feedback counselling; clubs; and integration with other services such as gender-based violence prevention. At the time of the summit, uptake varied across regions with a range of 36-98%. PrEP uptake is enhanced when it's part of a broader prevention package that includes peer support, mobile services and convenient operating times. The importance of training and clarifying health care worker attitudes in prescribing PrEP is critical. The integration of PrEP as part of a sexual reproductive health package has also been invaluable. Work has also focused on ways to reduce the burden of repeated visits for users, particularly because this will be rolled-out for healthy populations.

It is predicted that PrEP uptake in this region will be variable and likely evolve over time. The clinical trial platform could enhance these efforts and so trial staff should be trained and encouraged to offer PrEP. Trialists should agree on an adequate package for adherence support and recognize that patterns of PrEP use will most likely vary over the course of a trial.

Deliberations from community stakeholders

Advocacy groups play a critical role in HIV vaccine and prevention research. Community advocates and Community Advisory Board (CAB) members made several recommendations about PrEP provision in South Africa, which are summarised in Table 1.

Table 1 . Recommendations from community stakeholders.

• In South Africa, approx. 2,000 new HIV infections occur in young women each week; an alarming fact. If an effective agent against HIV acquisition exists, its use should not be put on hold.
• People need choices, not a one-size-fits-all approach. PrEP should be provided to participants who choose to take it either through easily accessible health care organizations/clinics in the region or by the clinical trial sites themselves.
• The SoC must be ethical, scientifically valid, and developed with sincere collaboration with communities and advocates.
• The SoC must be accountable, transparent, client-centred and provide mechanisms for advocates and community members to monitor and inform its evolution.
• Advocates and community representatives should be engaged in the design of the PrEP plans. Communities should feel 'ownership' rather than 'buy-in.'

C**onclusions**

The topic of how to use PrEP ethically, safely, and effectively has been a key consideration in planning the prevention trials currently taking place in or planned for South Africa. The use of PrEP, as with any new drug, is overseen by the South African Ministry of Health. The recommendations of the Ministry of Health, various South African ethics boards, research teams and ultimately the vulnerable community should be heeded in clinical trials conducted in South Africa. Consensus across all these stakeholders is important for deciding how and when to provide access to modalities that have not yet fully bloomed in-country.

This SoC summit took place at a watershed moment. South African investigators and collaborators including the NIH's two largest clinical trials networks working in South Africa, the HVTN and HIV Prevention Trials Network (HPTN), proposed to work together as the standard of prevention services change in southern Africa. PrEP is new, but this challenge is not. Similar conversations began in 2006, when voluntary medical male circumcision was shown to significantly prevent infection in men.

A number of recommendations arose from the summit: That the HIV prevention researchers move towards making PrEP available as part of the HIV prevention package for study participants of a clinical trial.

2. That investigators engage their government bodies or working groups to motivate the support of demonstration projects close to research sites.

In follow-up to the summit, the SAMRC, with additional support from the Fred Hutchinson Cancer Research Center (parent institution of the HVTN) and industry partners, set up a PrEP fund for drug acquisition and laboratory monitoring for HIV prevention studies across sub-Saharan Africa. This has enabled the SAMRC to purchase PrEP at state tender prices and utilise pre-existing negotiated laboratory contracts and within-study systems to extend available PrEP funds.

PrEP drug provision and related essential laboratory monitoring support has been initiated and is ongoing for interested and eligible HVTN efficacy trial participants at all 24 clinical trial sites that are conducting these trials (HVTN 702, HVTN 703/HPTN081 and HVTN 705/HPX2008). PrEP is now offered at each instance of risk reduction counselling along with other prevention methods provided during participant study visits and during the informed consent process. Where possible, sites may offer PrEP from their own pharmacies and staff are trained to prescribe and manage PrEP initiation and follow-up. Each clinical site has an up-to-date list of pharmacies and clinics that stock and prescribe PrEP in their areas. This will ensure that site staff can effectively counsel and refer participants who wish to participate in PrEP. PrEP training for site staff is offered periodically to enable PrEP prescribing and management.

This summit has demonstrated that considerations of SoC in a clinical trial setting is complex. These complexities may change and are subject to contextual nuances that may vary from site to site. There are guidelines, both locally and internationally, that can inform the review and the need to modify the standard of prevention to ensure clinical trials are performed with the highest ethical standards.

Competing interests

TK is a Member of the National Essential Medicines List Committee and a Guideline Methodologist for WHO. All other authors declare no conflicts of interest.

Authors' contributions

MDM wrote first draft and edited manuscript; LGB contributed to Summit organization and edited manuscript; TK contributed to Summit organization and edited manuscript; NB contributed to Summit organization and edited manuscript; LC contributed to Summit organization and edited manuscript; GEG contributed to Summit organization and edited manuscript. All authors have read and approved the final manuscript.

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