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Addressing standards of care in resource-limited settings

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Abstract

The choice between “best-known” standards of care (SOC) or “best available” standards as the control arm in the clinical trial is a fundamental dilemma in clinical research in resource limited settings (RLS). When the health system is delivering less than an optimal level of care, using highest SOC in a clinical trial may produce results that cannot be implemented or sustained locally. On the other hand, using interventions that are more feasible in the local setting may involve suboptimal care, and clinical outcomes may be affected. The need for improved standards in health systems in RLS, and the difficulty in securing them, has led many researchers advocate for policy changes at the national or international level to improve clinical care more systemically. SOC decisions in a clinical trial affect the level of benefit provided to study participants and the policy implications of the trial findings. SOC choices should provide high quality care to help advance the health care system in host countries participating in the trial, but balancing the scientific and ethical objectives of SOC choices is difficult, and there is no single formula for selecting the appropriate SOC. Despite the challenges, well-designed and conducted clinical trials can and should make significant contributions to health systems in RLS.

Keywords

standard of care; treatment guidelines; quality of care; HIV/AIDS; antiretroviral therapy; prevention

One of the most contentious topics of discussion involving clinical research in resource-limited settings (RLS) is the question of choosing an appropriate standard of care (SOC) for a clinical trial. The national, regional and local decisions about what represents SOC can affect comparator groups in clinical trials. Decisions about what represents the SOC, choice of comparator arms, and background care are complicated and have led to disagreements among clinical research stakeholders about what SOC should be chosen and why.

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Choosing the SOC in a clinical trial: best, local or new alternative SOC?

The strategies used to address SOC questions in different clinical trials vary widely. There are three approaches to trial design: 1) Evaluate proven regimens from high-income countries (HIC) in comparative effectiveness trials to determine best approaches in RLS; 2) test new, unproven interventions for use in populations in both HIC and low and middle-income countries (LMIC); or 3) study new unproven strategies in RLS using interventions expressly designed to address barriers to care that exist in RLS but do not exist in HIC.

National and international clinical guidelines differ in different countries and regions between HIC and LMIC. Until recently, US Department of Health and Human Services (DHHS) guidelines for antiretroviral (ARV) treatment[1] have recommended earlier initiation of treatment than the approach advocated by World Health Organization (WHO) guidelines.[2] Many national guidelines in LMIC may not immediately adopt most recent WHO standards for various reasons. Clinical trials taking place in both HIC and LMIC may allow for treatment initiation to vary according to national guidelines, while in others, a treatment threshold is set by the trial to ensure some level of consistency and to ensure that results will be relevant to emerging guidelines as treatment standards improve. Choosing SOC involves addressing the inevitable tension between trial designs that reflect the current policies or guidelines, and the improved clinical standards which one hopes will be adopted.

Determining the appropriate SOC often hinges on the research question itself. For example, study A5208[3] was designed to ask a research question uniquely applicable to RLS, namely, what treatment regimen is best for women who have previously been exposed to single dose nevirapine (sdNVP) for Prevention of Mother-to-Child Transmission (PMTCT)? The study arms consisted of the current SOC for ARV treatment at the time, versus an alternative regimen postulated to be superior in overcoming NVP resistance. This study helped improve the local SOC by addressing the unique healthcare context in the host country setting. The research question was not highly relevant for HIC where most women receive combination ART during pregnancy for PMTCT.

A new intervention may be an alternative one, neither best nor local SOC, specifically designed to overcome the barriers to implementing the best SOC. For example, single dose nevirapine (sdNVP) was developed as an intervention for women presenting for delivery without having had antenatal prophylactic ARVs. In HIC, SOC would have been combination ART during pregnancy and delivery, but at the time this was considered prohibitively costly in RLS. Additionally, women may present for labor without having had access to antenatal care—thus making it logistically impossible to initiate ART during pregnancy. Testing a sdNVP strategy therefore seemed a reasonable, feasible approach to provide substantial protection for PMTCT. Similarly, HIV-infected women could not safely formula feed, unlike in HIC, since it results in greater infant morbidity and mortality in RLS[4] and is not an appropriate intervention in that setting. Therefore, infant NVP prophylaxis and maternal triple ARVs have been tested for PMTCT during breastfeeding in RLS.

Specific SOC can be integrated into one or more of the trial arms through medical care that is background care, i.e. care that is part of the trial but is not the specific intervention being tested. For example, rifabutin might be used rather than rifampicin for TB treatment so that protease inhibitors (PIs) can be continued as a part of the ARV regimen being tested; or viral load monitoring may be required in the trial in order to assess ARV efficacy, even when it is not used in the local SOC. This means that clinical management in the research trial is not exactly comparable to the local SOC at the site, as in study A5175[5] (see Table 1). This can complicate interpretation and implementation of trial findings, since the intervention (e.g., HIV viral load monitoring, or use of rifabutin) might not be available outside the clinical trial.

Ancillary care is care that is not part of the trial and is unnecessary for its scientific aims—for example, referral for care or provision of care for conditions unrelated to the study.[6] This differs than "background care" which is important to the science of the clinical trial. An example of ancillary care would be referral for cancer screening in a trial of ARV treatment. Ancillary care can be an important motivator for trial participants to join and continue in a clinical trial because higher quality and more accessible care may be offered at research sites compared to surrounding communities.

Rationale for SOC choices

We explored the reasons for SOC choices in a number of case studies based on recent clinical trials (Table 1)[3,5,7–10]. The rationale for using best SOC is that either a) the findings *could* be used directly to spur LMIC implementation of the intervention(s) or b) the findings could drive advocacy, policy, or other efforts to overcome barriers to implementation. When lower or local SOC is used, barriers are viewed as significant and the trial is designed to generate findings that are broadly applicable without waiting for lengthy or even unreachable infrastructure, policy, financing or regulatory changes needed to introduce the best SOC. When a new intervention or strategy is developed to circumvent local barriers, the primary motivation is to develop a new SOC which is relevant, feasible, and responsive to LMIC needs. Table 2 provides examples of three approaches described above: local SOC, higher SOC and alternative SOC.

Barriers to achieving higher SOC

In choosing appropriate SOC for a trial, it is important to consider whether barriers to use of the higher SOC could be overcome in the near term. It is also ethically relevant to consider the anticipated health or cost effectiveness advantages of higher SOC versus the alternatives (How much clinical benefit? How significant?); whether the trial design can demonstrate convincing evidence to move policy decisions; and whether new or alternative SOC will be acceptable and feasible in the local setting.

Some barriers are more easily overcome than others. For example, a high-priced study drug may become more accessible when generic versions are available. In addition, while the high cost of some drugs often seems like the most insurmountable barrier to achieving higher SOC, in fact, the barriers may be multifaceted and complex, such as manufacturing shortages, supply chain issues, cold chain requirement, intellectual property (IP), licensing

issues, or product registration in the host countries. Just as significantly, health care infrastructure may be limiting: such as laboratory monitoring, equipment, or staff.[11] Patient and community level factors may also be barriers to higher SOC, including willingness to attend clinic and use the interventions, transportation barriers, and costs of care. Cultural stigma associated with HIV status, gender and sexuality and with "socially unacceptable" risk behaviors may affect these processes.

Thus, the barriers to achieving higher SOC in many countries cannot be reduced simply to the availability of a particular drug, and clinical trial design must take account of a complex range of economic, structural and social factors that influence what interventions can be made available to whom, at what cost, and with what level of benefit.

Background care in a research trial and local implications

The same considerations that apply to intervention arms also apply to decisions about background care, namely, feasibility and sustainability of implementing higher levels of care, and local relevance. The quality of background care also affects participant and community interests.

Experience in the field shows that study participants value the high quality care they receive at research sites;[12–14] and research staff develop relationships with and commitments to the study participants and their communities, which include a commitment to look after health care needs. When research teams develop training and infrastructure for enhanced clinical services at the research site and in the surrounding health care infrastructure, this can provide a lasting benefit and bolster long-term relationships between research organizations and host communities. Providing high quality care is a way of "giving back" to communities that have provided a cooperative environment for research to move the science forward, and available evidence shows that participants find this experience highly valuable.

In fact, the attractiveness of higher quality care at clinical trial sites can backfire in that research is so attractive that participants may be reluctant to reveal important clinical information which they fear would exclude them from the trial.[15,16] The attractiveness of research participation, with its consequences both positive and negative, is another indication that attention to the relationships of clinical research is imperative, in addition to considering the wider, global implications of trials.

Advocacy by researchers and other stakeholders for improved SOC

In doing clinical research that involves testing strategies that exceed what is available locally, the clinical investigators involved are caught in the tension between a local SOC that they know is suboptimal, and a test intervention that is potentially better, but not yet available or feasible. Some researchers have responded to these dilemmas by becoming local and national advocates for greater investment of resources to improve health care and public health infrastructure. When South African authorities refused to authorize the use of antiretroviral therapy for PMTCT and HIV treatment, even after these interventions were widely adopted worldwide, some clinical researchers in South Africa, notably Glenda Gray and James McIntyre, advocated vociferously for policy changes to bring these interventions

to the South African public health system. For many patients in South Africa at that time, enrolling in research studies was the only way to access effective care for HIV. Researchers like Gray and McIntyre were not conducting clinical trials to take advantage of lower SOC, but precisely the opposite: they were highly committed to developing the evidence to drive policy changes.

While ultimately the South African policies for ARV treatment and prevention were harmonized with international standards, there are other situations where country programs and policies remain at odds with accepted standards. For example, in some countries, lack of opioid substitution therapy for intravenous drug users (IDU) puts HIV prevention researchers in a quandary: using methods that are locally relevant means forgoing the known benefits of opioid substitution, whereas research studies incorporating these interventions risk being irrelevant to the local health system. When public health decisions appear to be based on biased views about certain interventions, rather than on a rational cost-benefit analysis, it is more difficult to justify omitting the interventions in a clinical trial. Still, the mixture of economic, social and policy factors that underlie these SOC decisions in different countries can be exceedingly difficult to untangle, and even more difficult to change when advocating for approaches with higher SOC.

Implications for research ethics

Investigators must continue to strive for research that can provide evidence to improve SOC, without losing sight of the need for trial results to be relevant to host country health systems. Researchers must maintain firm commitments to high quality care for trial participants, while ensuring that trial integrity and feasibility is maintained and that the trial results will be relevant. Research which makes no contribution to advancements of suboptimal local health care and health systems serves to perpetuate the injustice that these global health disparities represent.

Clinical research contributes to change in the SOC in various complex ways. Even when clinical trials demonstrate that a new SOC or higher SOC produces better results, the pathway from research to implementation is long and uncertain. Research itself can be a significant driver of policy change, but many other political and economic factors affect these policy decisions.

Researchers often seek to test improved levels of care to stimulate improvements in the health system. Yet when using higher standards in a trial, findings may be difficult to implement locally, and researchers need to consider a plan to transition to adequate levels of care after the trial. Ideally, researchers should engage with local or national health authorities to implement a SOC defined by research results within a reasonable time after the trial findings are available. In the case of A5175, national ARV programs were being set up at the time of the trial, so the study was poised to inform treatment programs in the host countries. This provided an ideal mechanism to secure ongoing access to care for patients and timely implementation of trial results.

The high quality care offered at most research sites makes clinical trial participation highly attractive for many potential participants. Some commentators worry that this appeal will

constitute an "undue inducement"[17,18] that will lead participants to decide to join a trial "against their better judgment," if, for example, they discount the risks of research in their eagerness to access the benefits.[19] Evidence so far indicates that participants are usually aware of clinical trial risks. Furthermore, in many phase III trials in RLS, such as the studies we describe here, the risks of the trials are similar to risks of standard care, especially in trials evaluating interventions that have already been studied elsewhere. In trials such as these, the trial objectively provides good quality clinical care and decisions to join such a trial are quite rational.

In trials of unproven interventions that may not be beneficial, the ethical calculus becomes complicated. In RLS, a prospective participant can choose local clinical care, which may not be optimal, or trial participation that offers higher quality care. But when there is a real possibility that the study intervention itself might be ineffective or even harmful, participants face a difficult tradeoff: the certainty of locally available care (with all its limitations) versus possible (but uncertain) risks and possible (but uncertain) benefits of a research study. Some have argued that worries about undue inducement are generally unfounded because IRBs should have already determined that the risk/benefit ratio of each study is ethically acceptable—so the attractiveness of the study should pose no threat to the interests of trial participants.[20] But this analysis overlooks the effects of local context in this equation. The very real deficiencies in access to health care do sway some individuals to join a trial, even if their preferences might otherwise be to avoid uncertainty and exposure to possible risks.

Conclusion

SOC decisions have been difficult and contentious in international clinical research. There is no single approach to SOC that is guaranteed to be scientifically and ethically sound; each study must be evaluated in light of the research question, the potential benefits to participants, the existing SOC, barriers to higher SOC, and the policy landscape. The ultimate goal is to conduct clinical trials that make a contribution to the advancement of clinical care in the host countries where they are conducted. Achieving these kinds of trial results and putting them into practice remains a daunting challenge. In spite of the challenges, well-designed and conducted clinical trials that provide the evidence base for improvements to SOC in RLS can stimulate significant and lasting advances in global health.

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Table 1

Case studies: Standard of Care in comparator arms in clinical trials

Name of trial	Intervention/ condition	Status quo SOC at trial initiation	Control arm(s)	Investigational arm(s)	Findings/ implications
A5208[3]:	Optimal Combined Therapy After single dose nevirapine Exposure for the prevention of mother-to-child transmission (PMTCT)	3TC/ZDV or FTC/TDF plus NVP	FTC/TDF + NVP	FTC/TDF + LPV/r	The LPV/r-containing arm was superior. Host countries adopted new treatment policies for women previously treated with sdNVP
A5175[5]	First line ARV regimens	3TC/ZDV plus EFV or NVP	3TC/ZDV + EFV	FTC/TDF + EFV ddI + FTC + ATV	The TDF-containing regimens were equally effective and safer; the ddI/FTC/ATV regimen was inferior to the other two regimens. FTC/TDF + EFV was widely adopted as first line regimen
PEPI-Malawi[10] SWEN[7] HPTN 046[9]	HIV prevention during breastfeeding for infants born to HIV-infected mothers	Official SOC recommendations changed during the conduct of trials. Formula feeding was recommended until excess mortality was detected, then early weaning and finally extended breast feeding was considered the best solution. No ARV breastfeeding interventions had been proven when PEPI was initiated. During the conduct of SWEN and HPTN 046, NVP prophylaxis was not implemented as SOC in any country	PEPI: placebo SWEN: placebo HPTN 046: placebo initially, trial modified to include 6 week NVP control arm after SWEN results became available	PEPI: 12 weeks infant NVP SWEN: 6 weeks infant NVP HPTN 046: 6 months NVP	All these interventions were designed to address HIV exposure during breastfeeding. In high-income countries, HIV-infected mothers use formula and do not breastfeed, but formula is not safe or feasible in RLS. Following release of the study results, infant NVP during breastfeeding was adopted in the WHO guidelines for PMTCT in 2009.

Abbreviations:
SOC = Standard of Care
ARV = Antiretroviral
3TC = lamivudine
ddI = didanosine
FTC = emtricitabine
TDF = tenofovir
EFV =efavirenz
NVP = nevirapine
LPV/r = lopinavir/ritonavir

Table 2

Case studies: SOC in background care at research sites

Trial	Research question/interventions	Background care offered at sites	Locally available care outside the trial	Implications of trial (local, or national)
VOICE [NCT00270257]	Safety and effectiveness of oral and vaginal Pre-Exposure Prophylaxis in women comparing tenofovir gel, oral tenofovir or Truvada	Comprehensive HIV prevention services (counseling, condom provision) and monthly HIV testing. Hormonal contraception & monthly pregnancy testing. Screening and treatment for sexually transmitted infections (STI) & clinical/diagnostic evaluation for symptoms. Referral to care if HIV detected	Routine self-directed HIV testing & counseling. Contraception through family planning services. Syndromic management of STI-related conditions.	Ease of contraception delivery was a major advantage according to women participants. Prompt & specific treatment of newly diagnosed STI. More frequent HIV testing undoubtedly allowed for detection of infection earlier than would have otherwise occurred, with consequent referral to care.
HPTN 058 NCT00270257	Effectiveness of drug and risk reduction counseling combined with either substitution drug treatment with buprenorphine/naloxone (BUP/NX) or short-term detoxification with BUP/NX	Behavioral and drug risk reduction counseling provided as part of both study arms. Routine blood testing and hepatitis B and C screening. Referral for care as needed.	No counseling available outside trial. Routine blood testing not available for IDU.	Counseling was included in both arms of the trial and did not exist outside research environment. Opiate substitution was not used in the health systems when the trial started, but the trial helped stimulate policy changes at national level in one country to include opiate substitution.
HPTN 052[8]	Early versus delayed initiation of ARV for the prevention of HIV transmission in discordant couples	Initiation of ARV therapy in the delayed arm was according to WHO guidelines, i.e. CD4 count < 250 cells/mm^3 at the time of the trial initiation. HIV primary care was offered in the trial sites according to clinical guidelines for prophylactic and symptomatic treatment for HIV/AIDS-related opportunistic infections, also screening for STDs throughout the study. All disease and conditions found during the study were treated or referred for care as appropriate.	Primary care services in the study were likely to be enhanced and more accessible relative to local standards. Regular clinical monitoring and laboratory testing may have exceeded what was locally available.	While all sites had ARV treatment available outside the clinical trial, the enhanced services and access to care may have been attractive for study participants. Early ART initiation reduced linked sexual transmissions by 96%: this was a landmark trial that effectively changed clinical practice globally.