

Pre-exposure prophylaxis
research
a quantitative ethics appraisal

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Background

- HIV pre-exposure prophylaxis = PrEP
- PrEP is an experimental biomedical approach for HIV prevention
- Therapeutic antiretrovirals might be able to prevent primary infection
 - *treatment of seronegatives (before exposure to HIV)*
 - *animal studies, PEP, PMTCT*
- PrEP could help curb the HIV epidemic
 - *modeling studies*
- Investments in PrEP have been increasing and expectations are high

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**19 HIV PrEP
prospective controlled trials
in humans**

Background

	INVESTIGATOR	SIZE	POPULATION	PHASE	HOST COUNTRY(IES)
x	Jackson	33	mixed	I/II	USA
x	Peterson	936	women	II	Cameroon,Ghana,Nigeria
x	Page Shafer	960*	women	II/III	Cambodia
	Grohskopf	400	MSMs	II	USA
	Choopanya	2,400	IDUs	II/III	Thailand
x	Hoffman	400*	men	II/III	Malawi
x	Smith	71	men, women	II/III	Botswana
	Thigpen	1,200	men, women	III	Botswana
	Grant	3,000	MSMs	III	Brazil,Ecuador,Peru,South Africa,Thailand,USA
	Celum	3,900	± couples	III	Kenya, Uganda
	Hendrix	144	women	II	South Africa,Uganda,USA
	Van Damme	3,900	women	III	Kenya,Malawi,South Africa,Tanzania
	Chirenje	4,200	women	II/III	Malawi,South Africa,Uganda,Zambia,Zimbabwe
	Grosskurth	72	± couples	I/II	Uganda
	Mutua	72	men, women	I/II	Kenya
	Anton	18	mixed	I	USA
■	Hosek	99	young MSMs	'preparedness [to be determined]	USA
■	HPTN 066	60	?	?	USA
■	HPTN 067	360	women, MSMs	?	Thailand?African countries?

x = closed study
■ = planned study
* = never enrolled



Background

- HIV PrEP is a promising approach but clinical trials are challenging
- 5 study sites were closed early based on ethics or methods considerations
 - Cambodia (2004); Cameroon, Nigeria & Malawi (2005), Botswana (2007)
- In response to these, guidelines for ethics and methods were proposed
 - for non vaccine HIV biomedical prevention approaches, including PrEP

UNAIDS/WHO, 2007
19 guidance points



Institute of Medicine (IOM), 2008
43 recommendations



Objectives

Based on HIV PrEP study-related documents:

- To appraise documentation quality of ethics considerations.
- To identify the least and most documented ethics considerations.
- To assess time trends in documentation of ethics considerations.

Methods

- **Source documents reviewed**
 - trial registry files
 - approved protocols
 - approved consent forms
 - study reports
- **Systematic ethics appraisal**
 - review of UNAIDS 19 guidance points & IOM 43 recommendations
 - derivation of ethics considerations relevant to PrEP (101 items)
 - 101 non redundant ethics considerations used as checklist data items
 - data items matched to 8 ethics principles (Emanuel et al., 2004*)

Methods

8 principles

COLLABORATIVE PARTNERSHIP 20 items

local collaborators involved as equals

FAVORABLE RISK-BENEFIT RATIO 4 items

benefits for participants outweigh risks

SOCIAL VALUE 7 items

clear benefits for host communities

INDEPENDENT REVIEW 10 items

transparency and competence

SCIENTIFIC VALIDITY 33 items

feasibility and acceptability of methods

INFORMED CONSENT 12 items

free and culturally appropriate consent

FAIR SELECTION OF STUDY PARTICIPANTS 6 items

based on validity and risk minimization

**RESPECT FOR STUDY PARTICIPANTS &
STUDY COMMUNITY 9 items**

standard of care, privacy and disclosures

number of checklist items matched to each of Emanuel et al.'s principles



Methods

descriptive statistics

- **At the study level**
 - proportion of items documented, overall
 - proportion of items documented, for each of the 8 principles
- **All studies considered**
 - number of study teams documenting each item*
 - median proportion of items documented, overall
 - median proportion of items documented, for each of the 8 principles
- **Adjustment of proportions**
 - items non applicable to a given study were not considered in denominator
 - we accounted for the number of items under each principle
 - *direct standardization (all principles assumed equivalent)*

* not presented here



14 HIV PrEP studies analyzed

Results

INVESTIGATOR	SIZE	POPULATION	PHASE	HOST COUNTRY(IES)
Jackson	33	mixed	I/II	USA
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presented as one study in information source

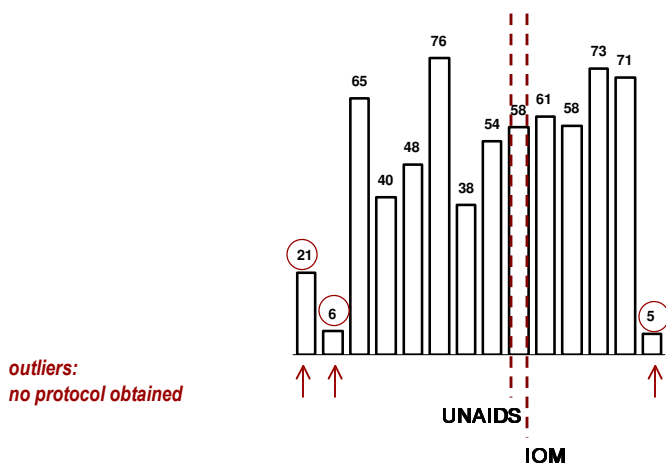
SOURCES:

13 registry files; 11 approved protocols; 11 approved consent forms; 3 reports



Results

study level: overall proportions

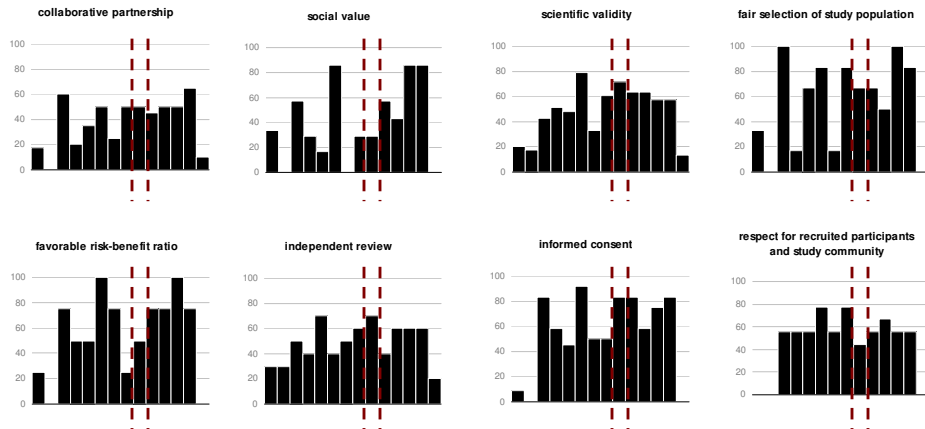


each bar represents the proportion of items documented for a given study (chronologically ordered, based on documents' date)



Results

study level: proportions by principle

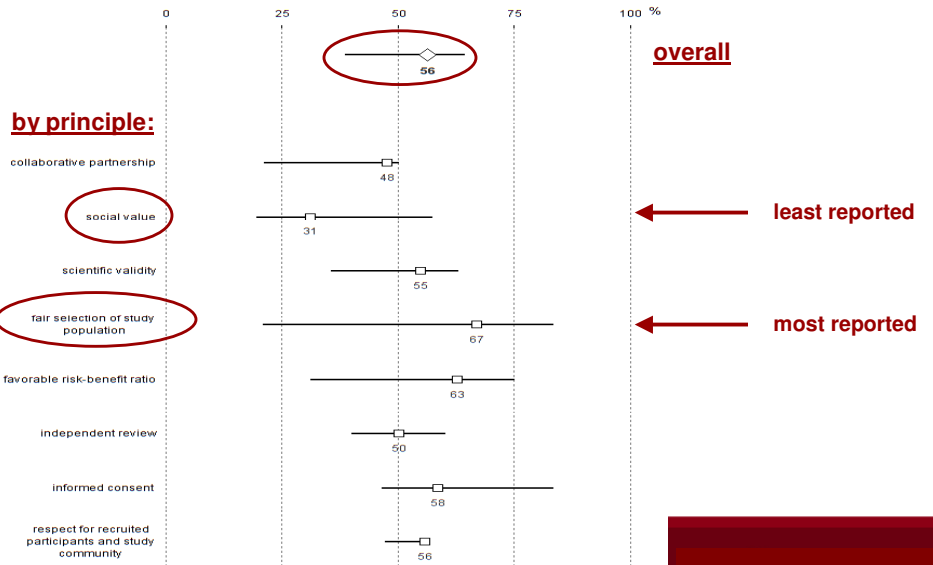


each bar represents the proportion of items documented for a given study (chronologically ordered, based on documents' date)



Results

across studies: median proportions



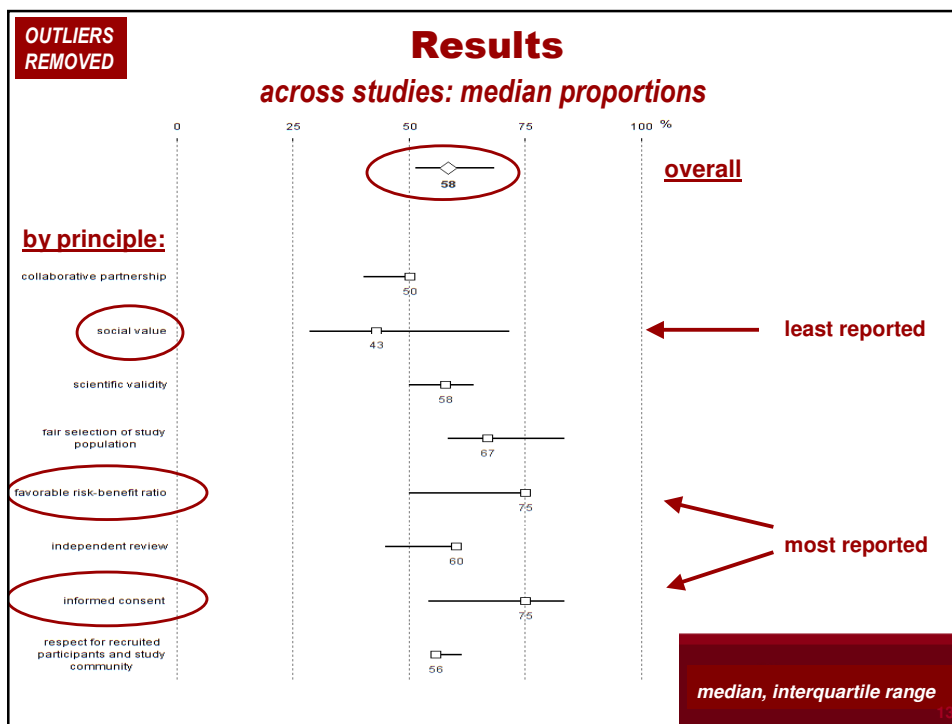
by principle:

overall

← least reported

← most reported

median, interquartile range



Discussion

- HIV PrEP investigators/sponsors were open to sharing study documents for this independent ethics appraisal.
- On average, at least 24% of the ethics considerations we pre-stated for this appraisal were not documented, at study level.
- Ethics related to social value were the least documented.
- We found variability in the documentation of ethics considerations. This was observed both across trials and across ethics principles.
- Some more recent PrEP studies had more ethics considerations documented than some earlier studies...but the opposite was also noted.
- We found no clear improvement in the proportions of documented ethics considerations in documents produced after the publication of the UNAIDS and the IOM guidelines.

Usefulness & Limitations...

- This systematic appraisal helped minimize subjectivity
 - checklist items were based on relevant literature
 - checklist items and guidance for extraction were formulated *a priori*
 - full-text documents were independently appraised by 2 reviewers
 - there was a reconciliation process to resolve disagreements
 - extraction was based on common data items, which allowed for relatively objective comparisons across trials

...Usefulness & Limitations

- However, the checklist used for this appraisal was not formally validated
 - *should other or more study documents be reviewed?*
 - *is Emanuel et al.'s framework the most appropriate to use?*
 - *are all the items most relevant to HIV PrEP research?*
 - *are there too many items? are some relevant items missing?*
 - *are all items worth the same weight?*
 - *does each item truly reflect the principle it was matched to?*

Conclusion...

results should be interpreted with caution

- This appraisal was an attempt to assess documentation quality, not actual research conduct.
- Proportions of items documented may not be a useful statistic, in practice, for ethics appraisals.
- It might be too early to estimate the uptake of UNAIDS' and IOM's guidelines by HIV PrEP researchers, based on documentation.
- However, many specific recommendations appear to be considered in some recent study documents.

...Conclusion

in the future

- More involvement of social experts might need to be considered in designing & conducting HIV PrEP studies.
 - *this would help enhance acceptability and foster social justice*
- Normative ethics guidelines are valuable tools.
 - *uptake should be actively encouraged*
- Regulated ethics monitoring procedures might serve as an incentive to improve documentation of ethics considerations.
- Validated ethics-encompassing reporting guidelines for protocols could also be useful.

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Questions & Comments

