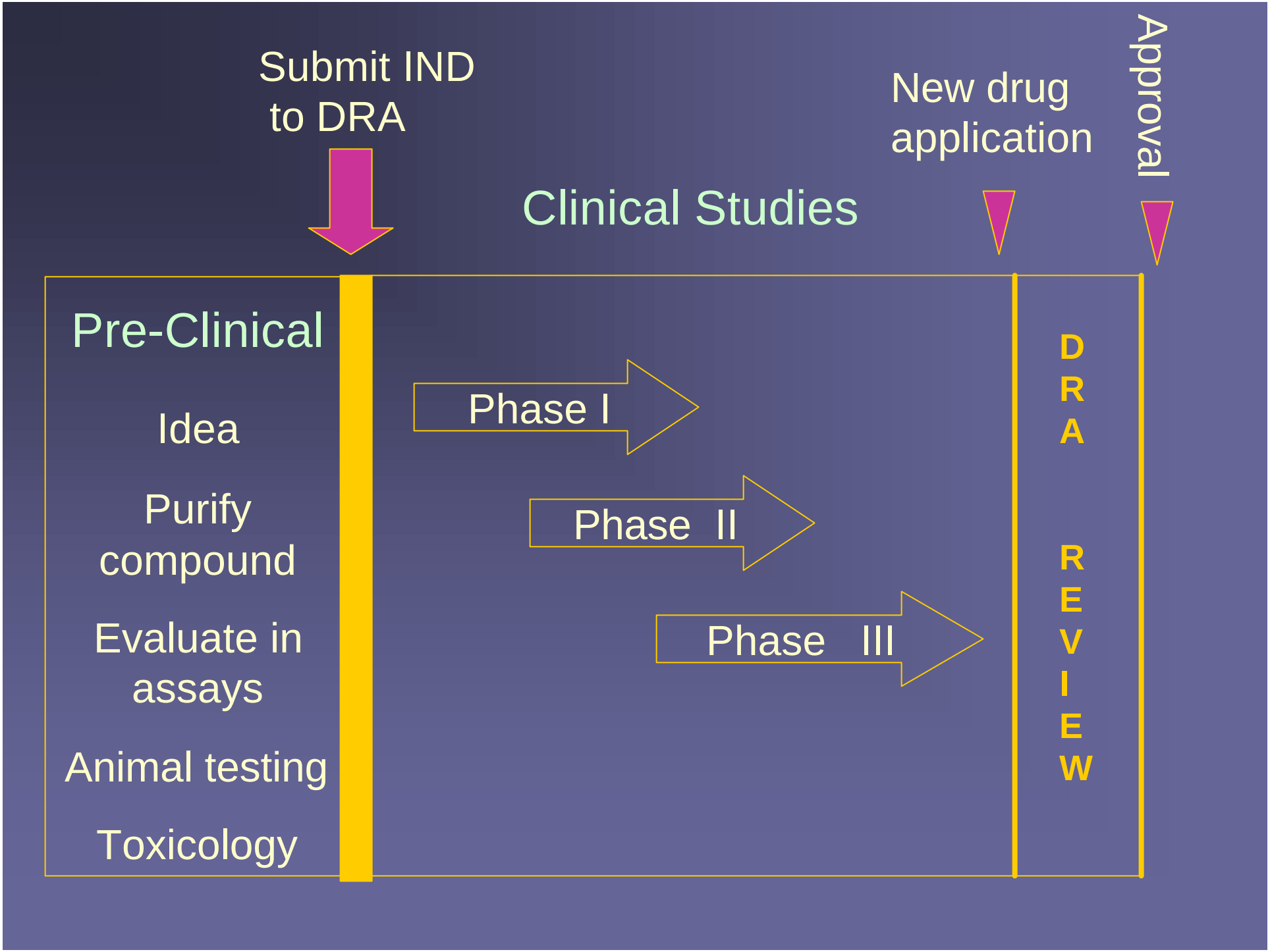
Overview of Microbicide Trials

Issues and Challenges

Special Challenges for Microbicides

- Complex clinical trial design
- New type of product
- Healthy volunteers
- Must be done among women at risk
- Disease remains stigmatized, fatal
- Sensitive issues – sex, power, ethics
- International collaborations


Submit IND
to DRA
New drug
application
Approval
Clinical Studies
Pre-Clinical
Idea
Purify
compound
Evaluate in
assays
Animal testing
Toxicology
Phase I
Phase II
Phase III
DRA
REVIEW

The Phases in Detail

	Number of Participants	Length	Purpose
Phase I	20 – 100	Several months	Safety
Phase II	~ 200 (male partners?)	6 months to 1 year	Expanded safety and acceptability
Phase III	3000 - 5000	1-4 years	Effectiveness

Drug development is slow & uncertain

	Duration (Years)	Chance of reaching the market (%)
Phase III Effectiveness	3	80
Phase II	2.5	50
Phase I Safety	1.5	20
Pre-Clinical Development	2.5	10

Clinical Trial Concepts: all phases

- **Informed Consent**
  - voluntary nature
  - does not affect care
  - risks/benefits
- **Standard of care**
  - care participants receive in trial

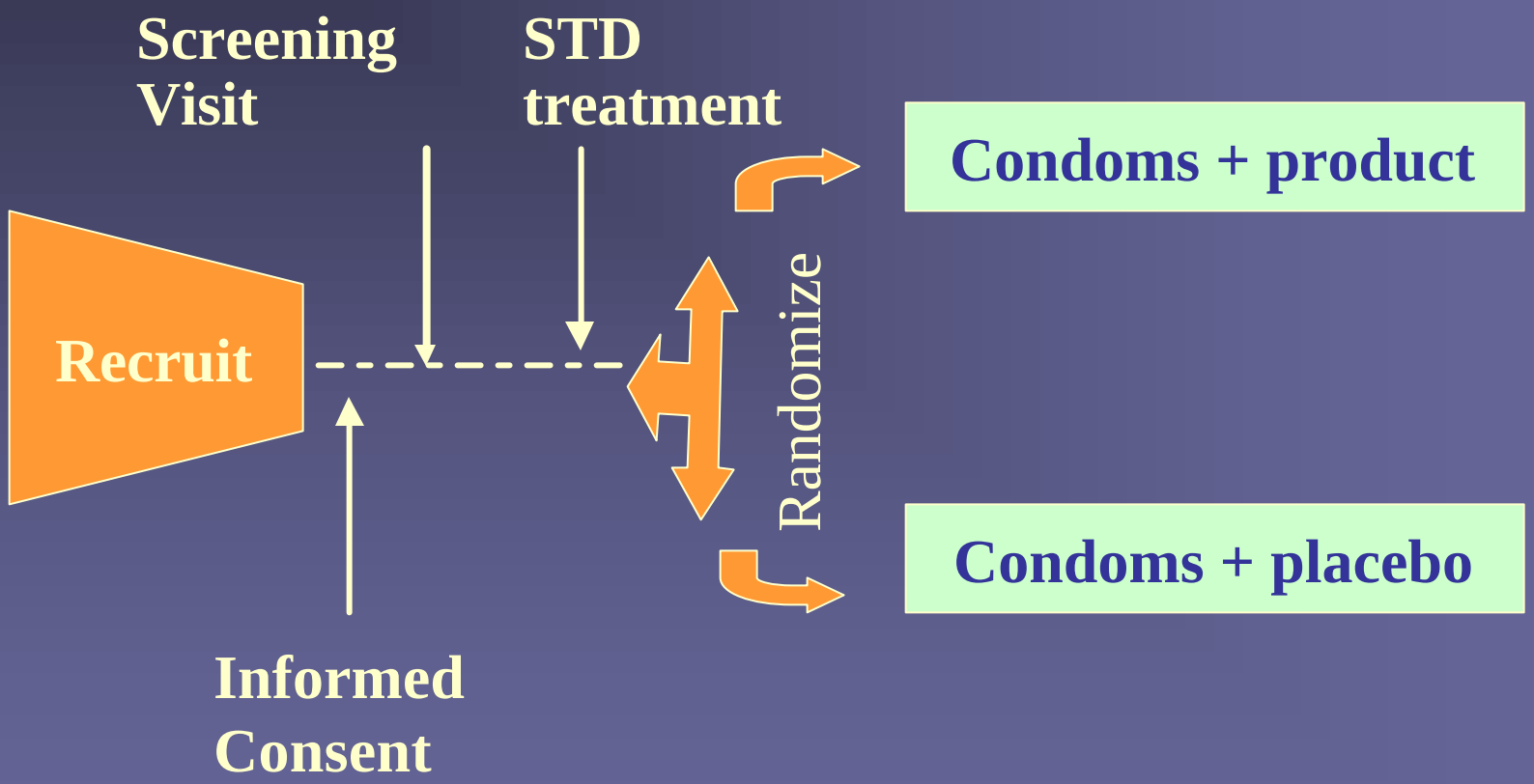
Clinical Trial Concepts (phase II/III)

- **Placebo**
  - mimics test product but without active ingredient
- **Double blind**
  - neither researchers nor participants know who is using which product
- **Randomization**
  - assign participants to study arms by chance
  - eliminate differences in groups (“bias”)

Designing a scientifically rigorous and ethically sound phase III trial

- Most rigorous design is randomized, double blind, placebo-controlled trial
- Unethical to withhold known HIV prevention
  - Participants in both active and placebo arms receive condoms, safer sex counseling, STI diagnosis and treatment
- Determine incremental benefit offered over condom use alone
- Attention to counseling, referral, informed consent

Basic Design for Microbicide Effectiveness Trials (Phase III)



Trials must be conducted in communities which have...

- ⇒ **research infrastructure**
  - laboratory facilities for HIV/STI diagnosis
  - clinics for physical exams
  - HIV testing and counseling
  - services and support for HIV+ persons
    - ?? ARV treatment??
- ⇒ **women at substantial risk of HIV infection through vaginal intercourse**
  - high incidence
  - little or no IVDU
  - large, relatively stable population

Sample size calculations for microbicides testing

Effectiveness	**Annual HIV Sero-Incidence**				
	1%	2%	3%	4%	5%
20%	110266	54638	36094	26824	21259
30%	46315	22965	15181	11289	8955
40%	24539	12176	8056	5995	4760
50%	**14736**	**7320**	**4847**	**3609**	**2868**
60%	9560	4753	3612	2351	1868
70%	6529	3249	2158	1612	1282
80%	4621	2304	1532	1144	913
90%	3353	1673	1115	835	666

Notes: Significance level = .05, power = 90%, test statistics and log rank test, two-tailed, equal size groups. Assumes 15 percent loss to follow-up. Figures prepared by Charlotte Ellertson and Kelly Blanchard of the Population Council using nQuery (version 1.0) survival analysis option.

Where do these communities exist?

- Most populations where women have high incidence are in developing countries
- In US and Europe, “high incidence” occurs in MSM; or is associated with IVDU
- *Most* large scale effectiveness trials are being established in developing countries
- Some Phase 1-2 safety testing in US/Europe
- All trials will require pooled data from more than one site

Limitations of testing

- Rare side effects can not be detected through clinical trials because hundreds of thousands of users need to use the product before rare events show up
- Therefore, post-marketing research and surveillance is important

Challenges

- Which study populations to enroll?
- Finding a true “placebo”
- Measuring product use
- Ensuring truly informed consent