

HIV vaccine research & development



Development of these overheads was made possible through funding from the European Commission (EC), and through the South African AIDS Vaccine Initiative (SAAVI), a lead programme of the South African Medical Research Council (MRC).



South African Medical Research Council

BUILDING A HEALTHY NATION THROUGH RESEARCH





Preventative, & therapeutic HIV vaccines

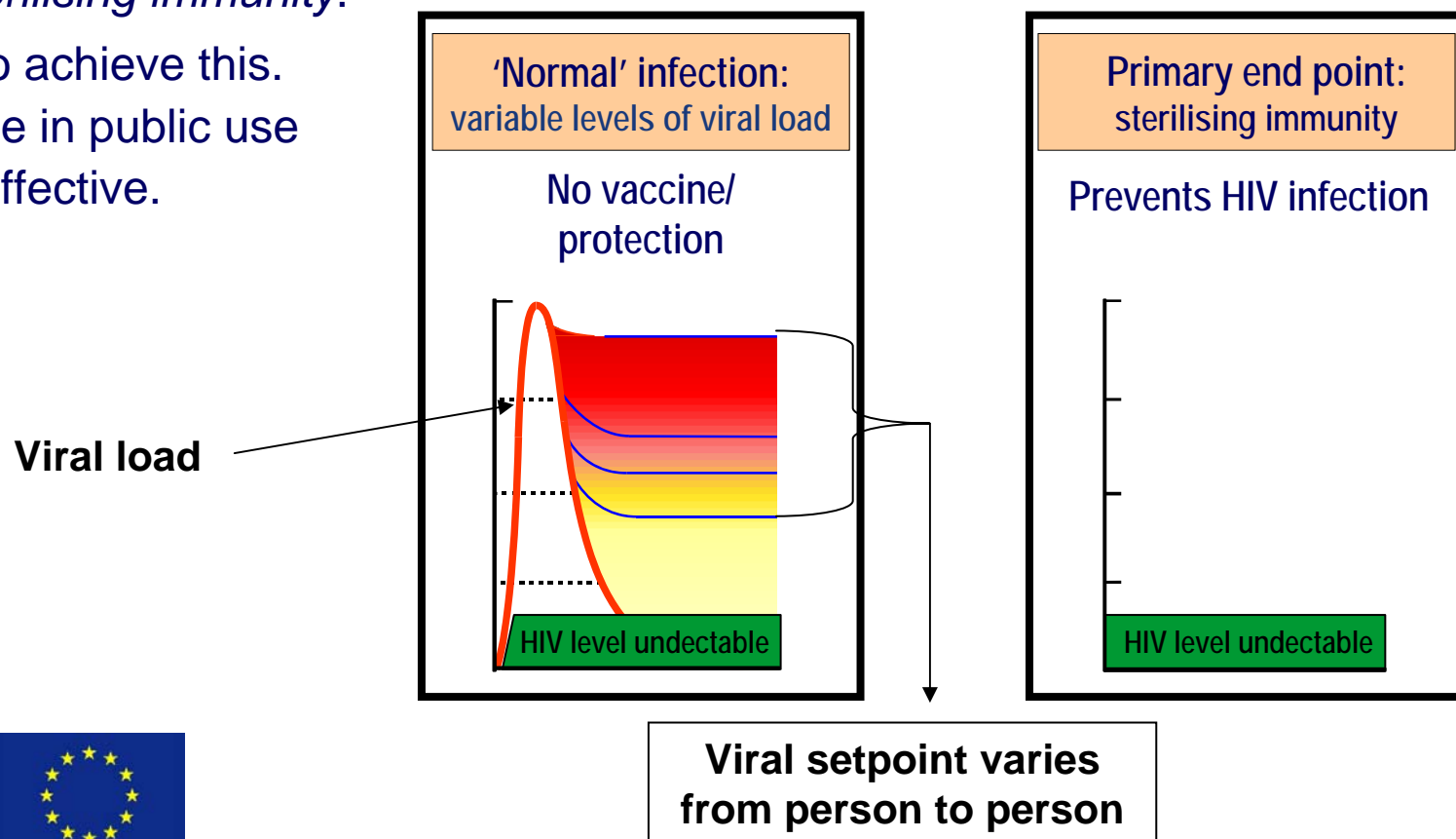
- A preventative HIV vaccine is tested in HIV-negative people to see:
 - if it will prevent HIV infection, or
 - stop, or slow disease progression if infection occurs.
- A therapeutic HIV vaccine is tested in people who are HIV-positive
 - to see if it will strengthen/boost their immune response against HIV.
- Aims to slow disease progression.





What is an effective preventative HIV vaccine? (1)

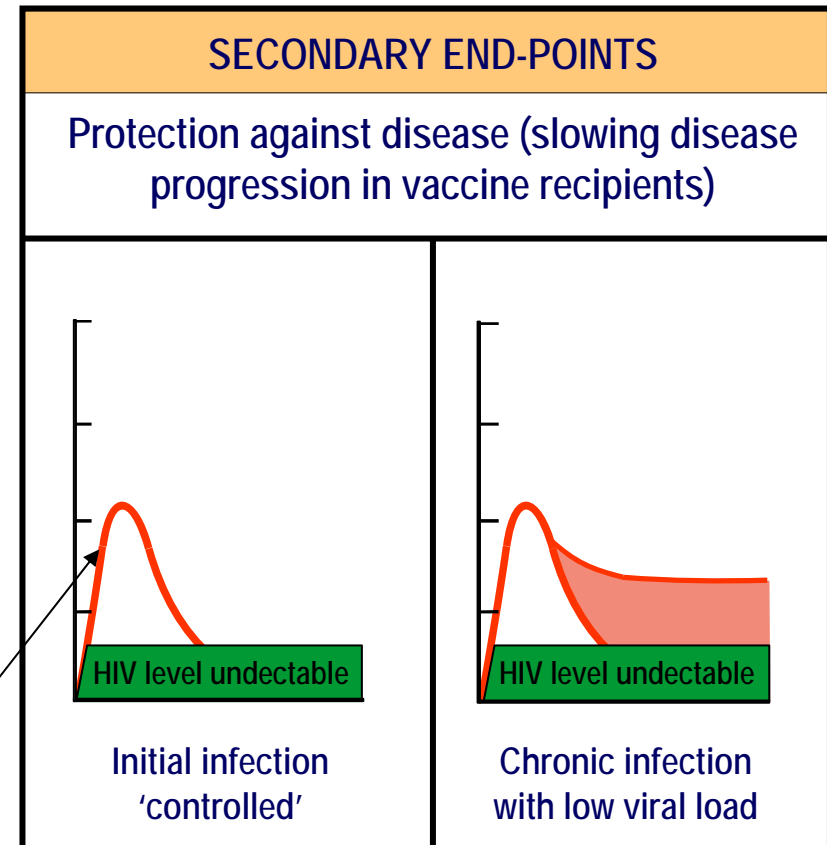
- 1st prize is a vaccine that prevents infection completely.
 - Called *sterilising immunity*.
 - Unlikely to achieve this. No vaccine in public use is 100% effective.





What is an effective preventative HIV vaccine? (2)

- 2nd best end-points are:
 - a vaccine that helps the immune system clear infection, or
 - a vaccine that results in better viral load control. This could mean that:
 - The vaccine helps to slow disease progression, and/or
 - The vaccine helps to reduce a person's level of infectiousness.



Viral load



What HIV vaccine designs are used?

- NO live-attenuated or whole-killed designs.
- NO whole or live HIV in the vaccine, so it cannot cause HIV infection.
- Only include one or more laboratory-made proteins, peptides or genes from HIV.
- Aim to create an immune response resulting in:
 - memory B- & or T-cells to trigger a quick immune response if they ‘see’ HIV in the future, or
 - boosting the existing immune response to HIV (therapeutic vaccines).





An HIV vaccine

- Like a car with its engine removed.
- Immune system sees it's a car by the 'outside parts'
 - the one or more laboratory-made proteins, peptides or genes from HIV.
- But it can't drive – the vaccine cannot HIV infection.
- Because it has no engine – no whole or live HIV.
- The vaccine causes the immune system boost the response to HIV (therapeutic vaccines) or to make B- & or T- memory cells (preventative vaccines).
- Memory cells stay on guard & cause a much quicker immune response to HIV if exposed to it in future.

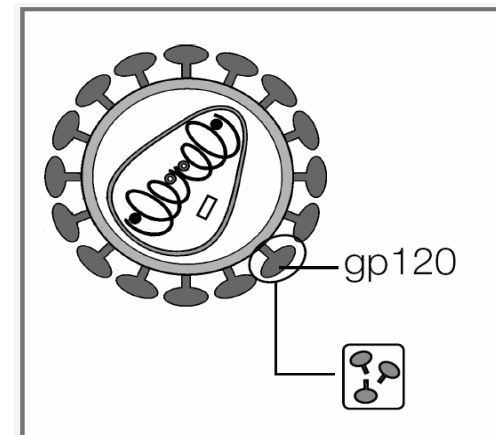


***An HIV vaccine is like a car
with its engine removed***



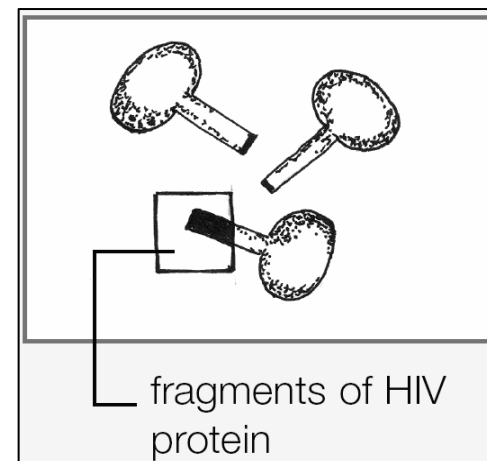
Recombinant subunit protein design

- Includes one or more laboratory-made proteins from HIV.
 - e.g. proteins from the envelope surface of HIV like gp120.
- Not taken from the actual virus.



Peptide vaccine design

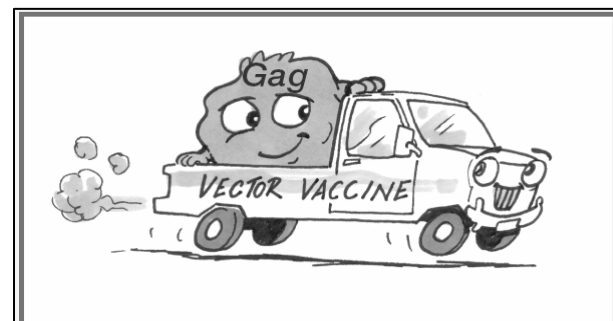
- Includes laboratory-made fragments of the HIV proteins to cause an immune response.



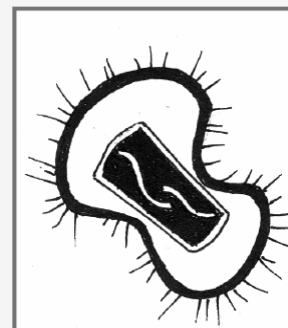


Vector vaccine design

- One or more harmless HIV genes
- Put into another type of virus or bacteria e.g. the cold virus.
- This germ is changed so it cannot cause harm.
- Called a vector (vehicle), it is used to carry the HIV genes into the body to cause an immune response.



Vector vaccines are like a car that is carrying a passenger.

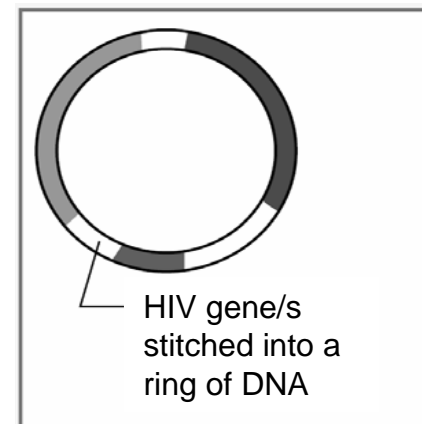


Vector vaccine using a bacteria that is changed



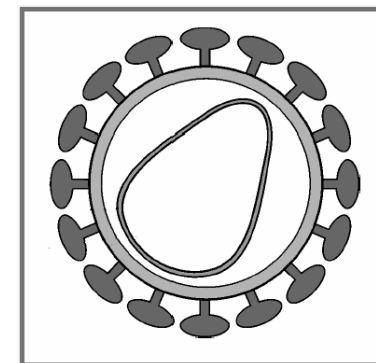
DNA vaccines

- One or more laboratory-made HIV genes are stitched into a ring of DNA from another germ.
- Called **plasmids**.
- South Africa has developed a candidate vaccine using this approach.



Pseudovirion/virus-like particle (VLP) design

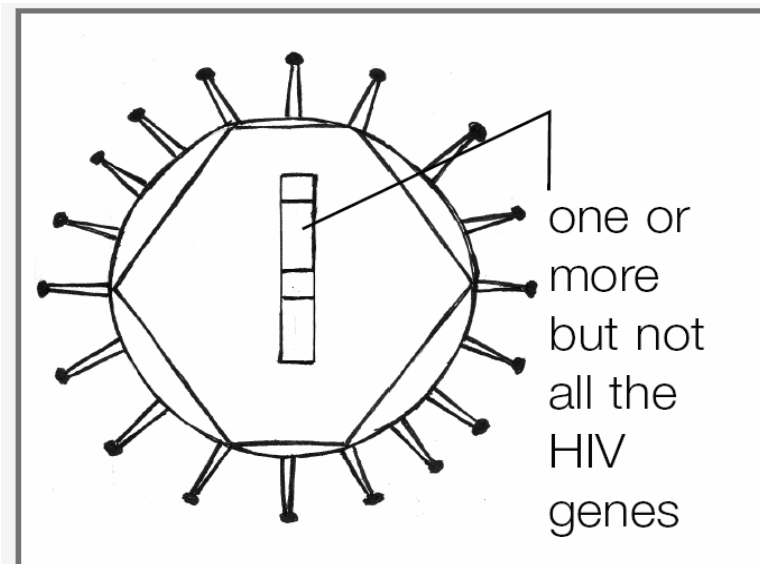
- Put some but not all HIV proteins together to look like an HI virus.
- Does not HIV genes, so it cannot multiply to cause infection.





Replicon vaccine design

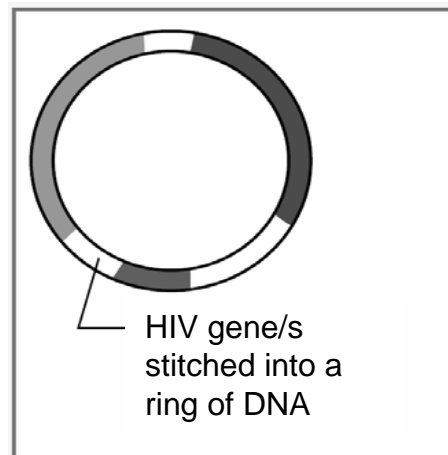
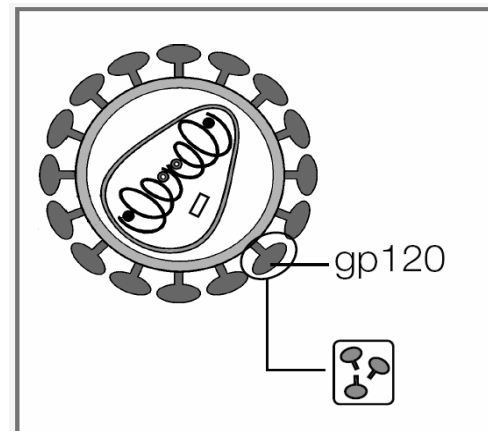
- Laboratory-made non-HI viruses.
 - Called **replicons**
- DNA removed from the virus.
 - Can't multiply or cause infection
- Replicons carry one or more laboratory-made HIV genes into the body to trigger an immune response.





Combination approach

- More than one HIV vaccine design given.
- **1st** primes the immune system, e.g. subunit protein vaccine.
- **2nd** boosts it, e.g. with a DNA vaccine.
- Think it will work better than using just one design.



e.g. subunit
protein vaccine
to **prime**



e.g. DNA vaccine
to **boost**



Why did it take so long to develop an HIV vaccine?

- Took a long time to understand how HIV works
 - 1981: first cases of rare illnesses now known as symptoms of AIDS
 - 1984: researchers finally found or isolated the germ responsible, HIV
- Could not use traditional vaccine designs
- No one has ever cleared HIV infection from their bodies
- Researchers are constantly learning more about HIV.
- They use this knowledge to develop new HIV vaccine designs



HIV vaccine clinical trials in humans

- Usually a randomised, double-blind, placebo-controlled research design
 - No one knows which group the participants are in. Otherwise, this knowledge could interfere with the research results.
 - All participants go through the same procedures & research steps.
 - Helps to ensure NO researcher or trial participant bias.
 - The only difference between the groups is the test HIV vaccine.
 - So any significant difference in results between the two groups can only be because of the vaccine.



Phase I clinical trials

What are the aims?	Who is involved?	How long?
<p>To test:</p> <ul style="list-style-type: none"> • mainly for safety; • tolerance - how acceptable the vaccine is to humans; • to a certain extent an immune response (immunogenicity). 	<p>Usually 40 to 120 people.</p> <p>In preventative healthy, HIV-negative, adults (over 18), at lower risk of HIV infection.</p> <p>In therapeutic trials, participants are HIV-positive. Usually people whose immune system is still relatively strong.</p>	<p>About 12–18 months to conduct the trial</p> <p>Plus 3–4 months to analyse the data & produce results.</p>
<p>If the test HIV vaccine is safe & looks promising, researchers can submit a protocol to the relevant bodies for approval of a phase II clinical trial.</p>		



Phase II clinical trials

What are the aims?	Who is involved?	How long?
<ul style="list-style-type: none"> • still to check safety & immunogenicity; • the best way of giving the vaccine, e.g. by injection under the skin, into the muscle; and, • when, how much, & how often to give the vaccine. 	<p>100s of participants.</p> <p>Preventative trials, involve healthy, HIV-negative adults, at low & high risk of infection. In South Africa, they may need at least 12 years education.</p> <p>Participants in therapeutic trials must be HIV-positive. Trials usually require people whose immune system is relatively strong.</p>	<p>Usually takes 1–2 years.</p> <p>Plus 4–6 months to analyse the data & to produce results.</p>
<p>If the results are promising, then researchers can apply to the relevant bodies for a phase IIb or a phase III trial.</p>		



Phase IIb clinical trials

What are the aims?	Who is involved?	How long?
<ul style="list-style-type: none"> • Test for efficacy – whether the vaccine works to prevent infection or to slow disease progression. • Always test for safety. 	<p>2000 - 3000 participants.</p> <p>Preventative trials, involve healthy, HIV-negative adults, at high risk of infection.</p> <p>Participants in therapeutic trials should be HIV-positive. Trials usually require people whose immune system is relatively strong.</p>	<p>Usually takes about 3-4 years.</p> <p>Plus 12-18 months to analyse data & produce results.</p>
<p>Results help researchers decide how to take research on the vaccine design further. It costs less than a phase III trial & is a good way to use limited resources.</p>		



Phase III clinical trials

What are the aims?	Who is involved?	How long?
<ul style="list-style-type: none"> • Test for vaccine efficacy – whether it works to prevent HIV infection or to slow disease progression. • Always to test for safety. 	<p>1000s of participants e.g. 10 000.</p> <p>Preventative trials, involve healthy, HIV-negative adults, at high risk of HIV infection.</p> <p>Participants in therapeutic trials should be HIV-positive. Usually require people whose immune system is relatively strong.</p>	<p>Usually 3-4 years.</p> <p>Plus 12-18 months to analyse data & produce results.</p> <p>May be interim results.</p> <p>3-4 years to follow up those with breakthrough infections.</p>
<p>If the vaccine is successful, researchers can apply to the regulatory authority to license it. They might also offer it to the group who got the placebo.</p>		



Phase IV

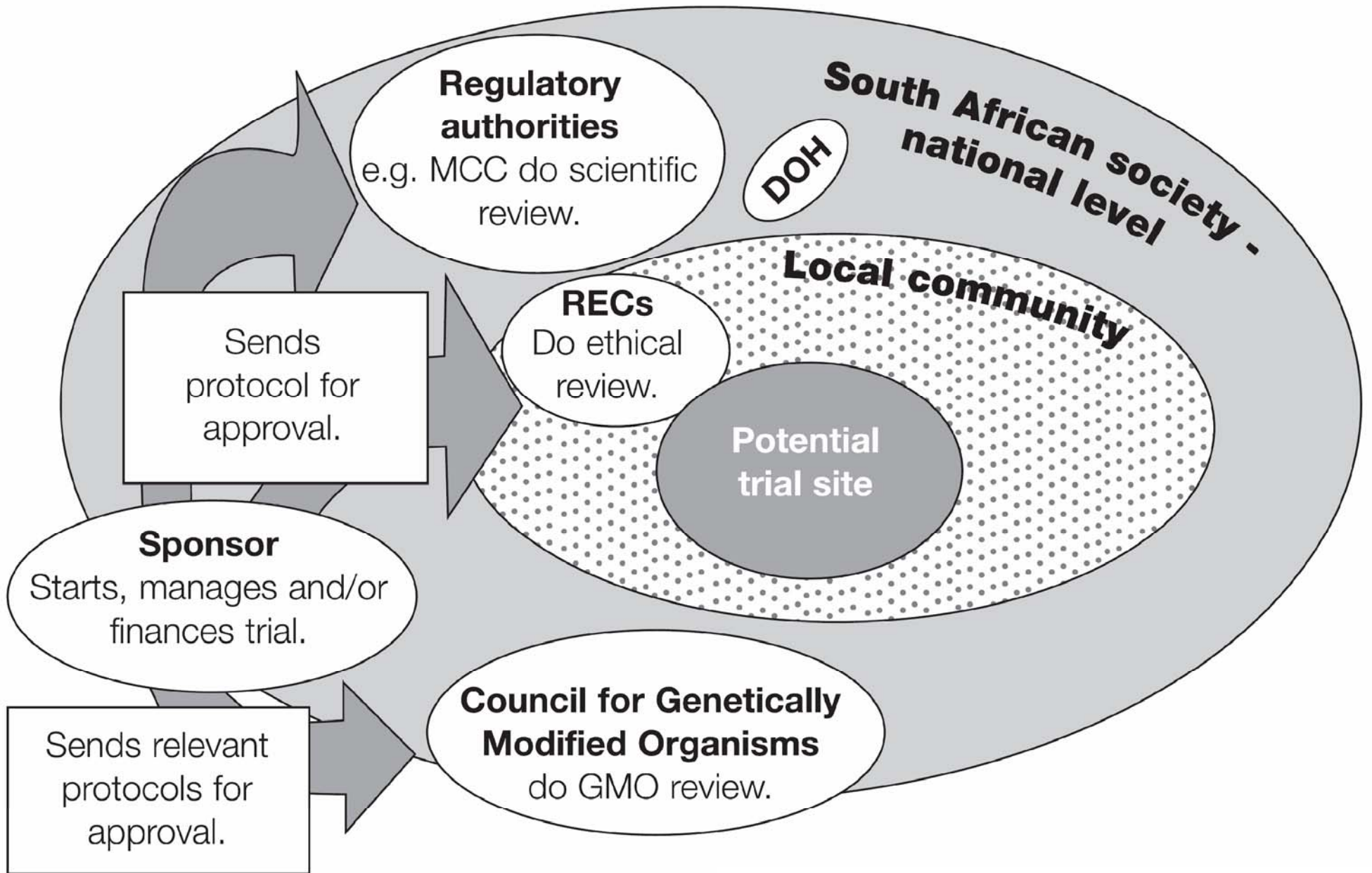
What are the aims?	Who is involved?	How long?
<ul style="list-style-type: none"> • Monitor how well it works in the general public under real-life conditions <ul style="list-style-type: none"> –e.g. when stored & transported on a big scale. • Any rare adverse drug reactions? • Does it reduce the number of new infections, or slow disease progression in members of the general public? 	<p>General public.</p>	<p>Several years to see the effect of the vaccine on the general public.</p> <p>Monitoring is ongoing.</p>
<p>Problems identified are addressed: e.g. better training for staff who administer the vaccine, more fridges to store, withdrawal of the vaccine if any very serious rare adverse drug reactions etc.</p>		

Also called post-licensure, or field studies



Parties involved in approving clinical trials

Parties	Description	Main role/s
Sponsor	The company, institution or organisation that starts, manages or finances the clinical trial.	They submit the protocol for approval to the regulatory authority/ies & the RECs.
Regulatory authorities	Independent body set up by government to regulate activities in an area using rules & standards.	e.g. the Medicines Control Council (MCC) of South Africa who do a scientific review of the protocol.
Research Ethics Committees (RECs)	An independent committee that is part of an academic or research organisation.	Includes academics and lay or community people, who review the protocol to ensure the trial is ethical.
Council of Genetically Modified Organisms	Ensure responsible development & production of GMOs.	Can approve/reject testing of HIV vaccine designs that use GMOs.



Parties involved in approving clinical trials



Parties involved in running clinical trials (1)

Parties	Description	Main role/s
Sponsor	The company, institution or organisation that starts, manages/finances the trial.	<ul style="list-style-type: none"> • Appoints qualified staff to design the protocol, manage the trial, analyse data, & write trial reports. • Ensures supply & instructions for vaccine & placebo. • Ensures safety & trial progress reports are regularly given to the regulatory authorities & the REC. • Ensures reports on SAEs are immediately sent to the PIs, RECs & regulatory authorities.
Principal Investigator (PI) Usually appointed by the Sponsor.	<ul style="list-style-type: none"> • Usually a medical doctor qualified to do the trial. • Local PI in multi-country trial. • Overall PI if many sites in one country. 	<ul style="list-style-type: none"> • Takes joint/ sole responsibility for designing, carrying out, analysing & reporting on the clinical trial. • Checks: trial is approved; site & staff are ready to start. • Must know & follow protocol, laws & guidelines, & ensure staff do too.



Parties involved in running clinical trials (2)

Parties	Description	Main role/s
Trial site Director/ Study Co-ordinator	<ul style="list-style-type: none"> • Usually a professional health care worker, e.g. a doctor. • Can also be the PI. 	<ul style="list-style-type: none"> • With PI, responsible for carrying out the trial & addressing problems. • Ensures the site functions efficiently & co-ordinates the day-to-day running of the trial. • Ensures trial is managed according to the protocol, relevant guidelines & laws. • Ensures trial participants have given IC & that confidentiality is kept.
Medical officers	Qualified doctors.	Do medical check-ups, make clinical decisions, evaluate laboratory results, report SAEs & follow them up.



Parties involved in running clinical trials (3)

Parties	Main role/s
Trial nurse/s	<ul style="list-style-type: none">• Helps medical officers to do examinations.• Takes blood & vital signs, e.g. blood pressure.• Completes Case Report Forms (CRFs)• May do counselling.
Pharmacist	<ul style="list-style-type: none">• Keeps a record of products, e.g. received & used.• Gives out or dispenses the bottles & explains how it should be given.
Data manager/s	Processes CRFs & data – puts info on computer.



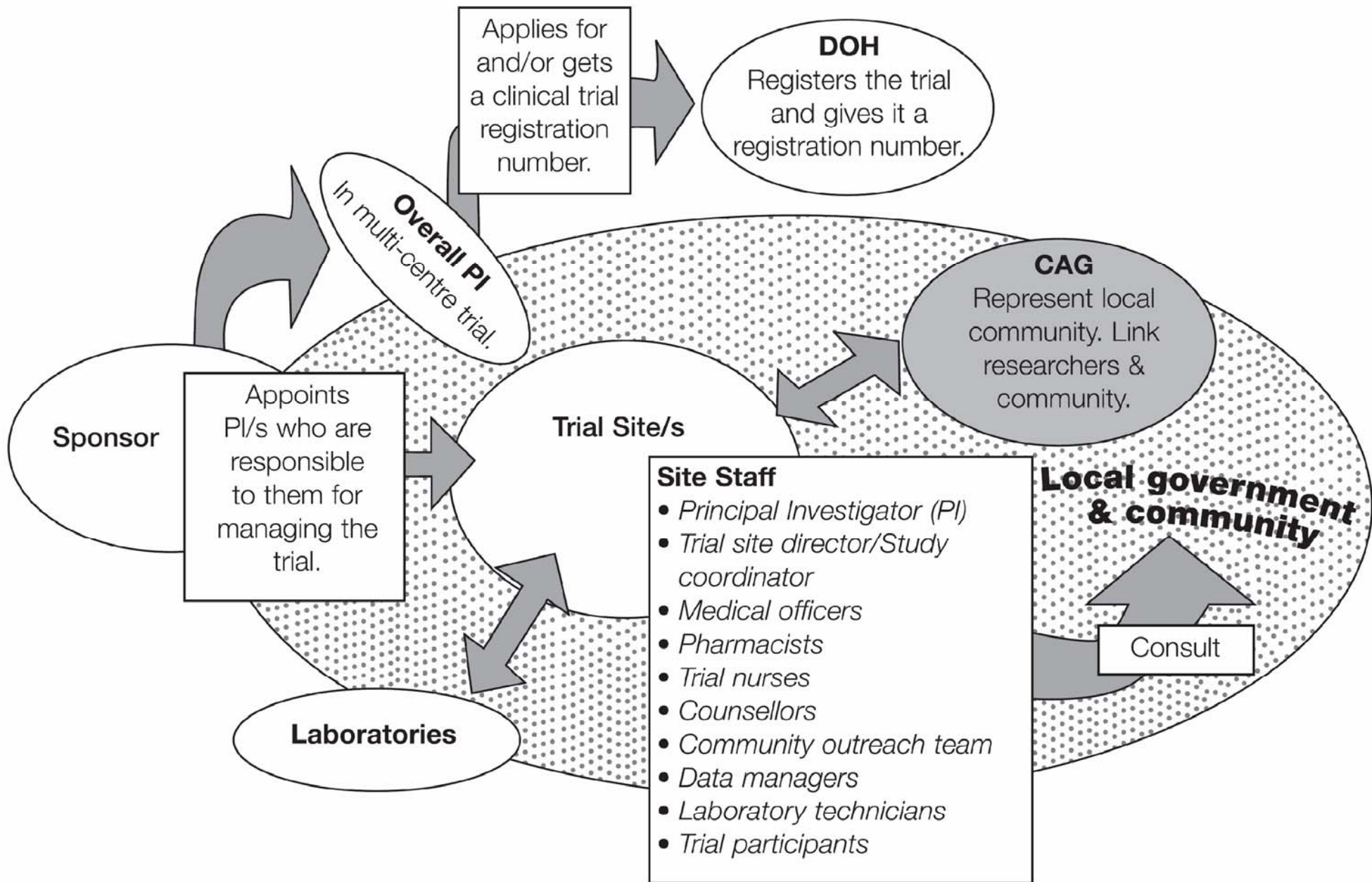
Parties involved in running clinical trials (4)

Parties	Description	Role
Counsellor/s		<ul style="list-style-type: none"> • Do pre- and post-test counselling, risk-reduction & pregnancy-reduction counselling. • Gives counselling & helps with informed consent.
Community outreach personnel	This team can include nurses, social scientists, counsellors & community educators.	<ul style="list-style-type: none"> • Responsible for communication between trial site & the community, and to recruit & retain trial participants. • Usually work closely with the Community Advisory Group (CAG)



Parties involved in running clinical trials (5)

Parties	Description	Main role/s
Laboratory technician	Based at the site.	<ul style="list-style-type: none"> • Test & analyse samples obtained from trial participants. • Where necessary prepare samples for transfer to outside laboratories for analysis.
Laboratories	Outside the site.	<ul style="list-style-type: none"> • Test & analyse samples the site is not equipped for. • Routine laboratories run standard tests e.g. pregnancy tests, HIV antibody tests. • Research laboratories do tests designed for the trial.
Community Advisory Group/Board (CAG/B)	Volunteers who live & work in the trial site area.	<ul style="list-style-type: none"> • Ongoing communication & advisory link between the community & researchers. Represent community interests & concerns. • Participates in decision-making to do with the trial that affects the community.



Parties involved in running clinical trials



What is quality assurance?

- Actions taken to ensure trials are of a high standard.
- This is done by checking that:
 - The rights & well being of trial participants are protected.
 - Information that is reported in the trial is accurate & complete.
 - The trial is run according to the protocol, guidelines, e.g. GCP, & other legal requirements.





Parties involved in quality assuring clinical trials (1)

Parties	Role
Sponsor	<ul style="list-style-type: none"> • Implements & maintains QA and quality control systems: <ul style="list-style-type: none"> – appoints Monitor, sometimes IDMC & Auditor, & develops SOPs. • Ensures trial site & laboratories allow access to parties who do QA. • Informs regulatory authority & RECs of serious violations of GCP.
PI	<ul style="list-style-type: none"> • Should allow access to trial site to parties who do QA. • Should be available for regular visits by the Monitor. • Confirms with Monitor that site follows the protocol & Sponsor's SOPs.
<p>The Monitor</p> <ul style="list-style-type: none"> • Has medical or pharmaceutical experience. • Important link between Sponsor & PIs. 	<ul style="list-style-type: none"> • Oversees & reports on trial progress & management to Sponsor. • Visits site regularly to ensure trial is done & reported according to the protocol, SOPs, laws & guidelines. • Should be available at all times for consultation or reporting of SAEs.



Parties involved in quality assuring clinical trials (2)

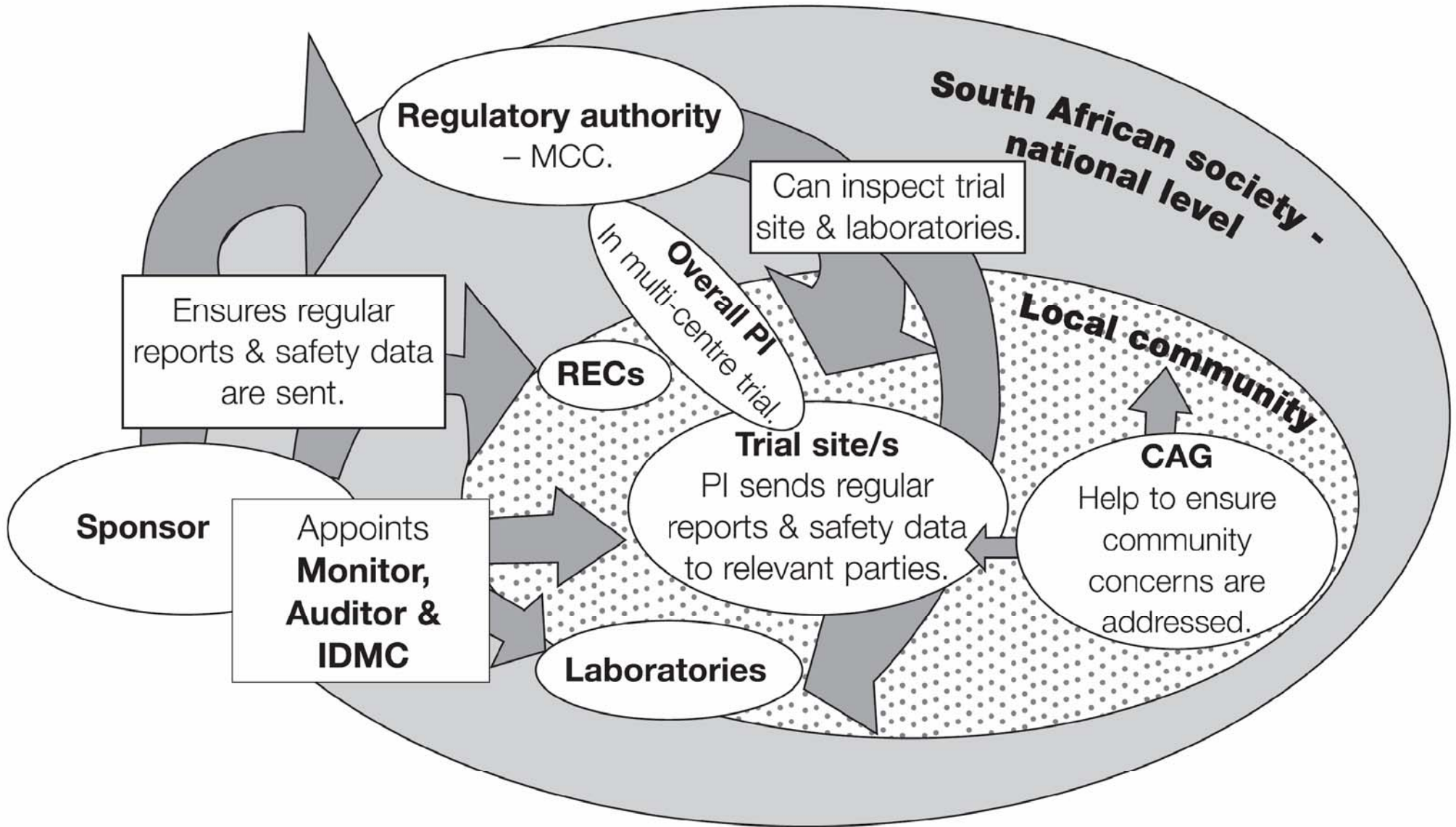
Parties	Description	Role
The Auditor	Independent person, organisation/group. Must be qualified to audit the trial.	<ul style="list-style-type: none"> • Does in-depth examination of the trial. • Checks if the trial meets the protocol, GCP, GLP & legal requirements.
RECs		<ul style="list-style-type: none"> • Review & monitor the trial in an ongoing way from an ethics & human rights point of view.
Independent Data-Monitoring Committee (IDMC) / Data Safety Monitoring Board (DSMB)	A committee of independent clinical researchers.	<ul style="list-style-type: none"> • Review data from the trial at different points to check trial progress. • Review safety data, and e.g. efficacy data in a phase III trial.



Parties involved in quality assuring clinical trials (3)

Parties	Main role/s
CAG/B	<ul style="list-style-type: none"> • Important ongoing communication link between the researchers & the community. • A mechanism to ensure that any human rights issues & other community concerns are addressed.
Medicines regulatory authority (in South Africa, the MCC)	<ul style="list-style-type: none"> • Can do on-site inspections at any time. • Compares the practices at the trial site with those in the protocol & in reports submitted to it, i.e.the MCC.





Parties involved in quality assuring clinical trials



How trial sites are chosen (1)

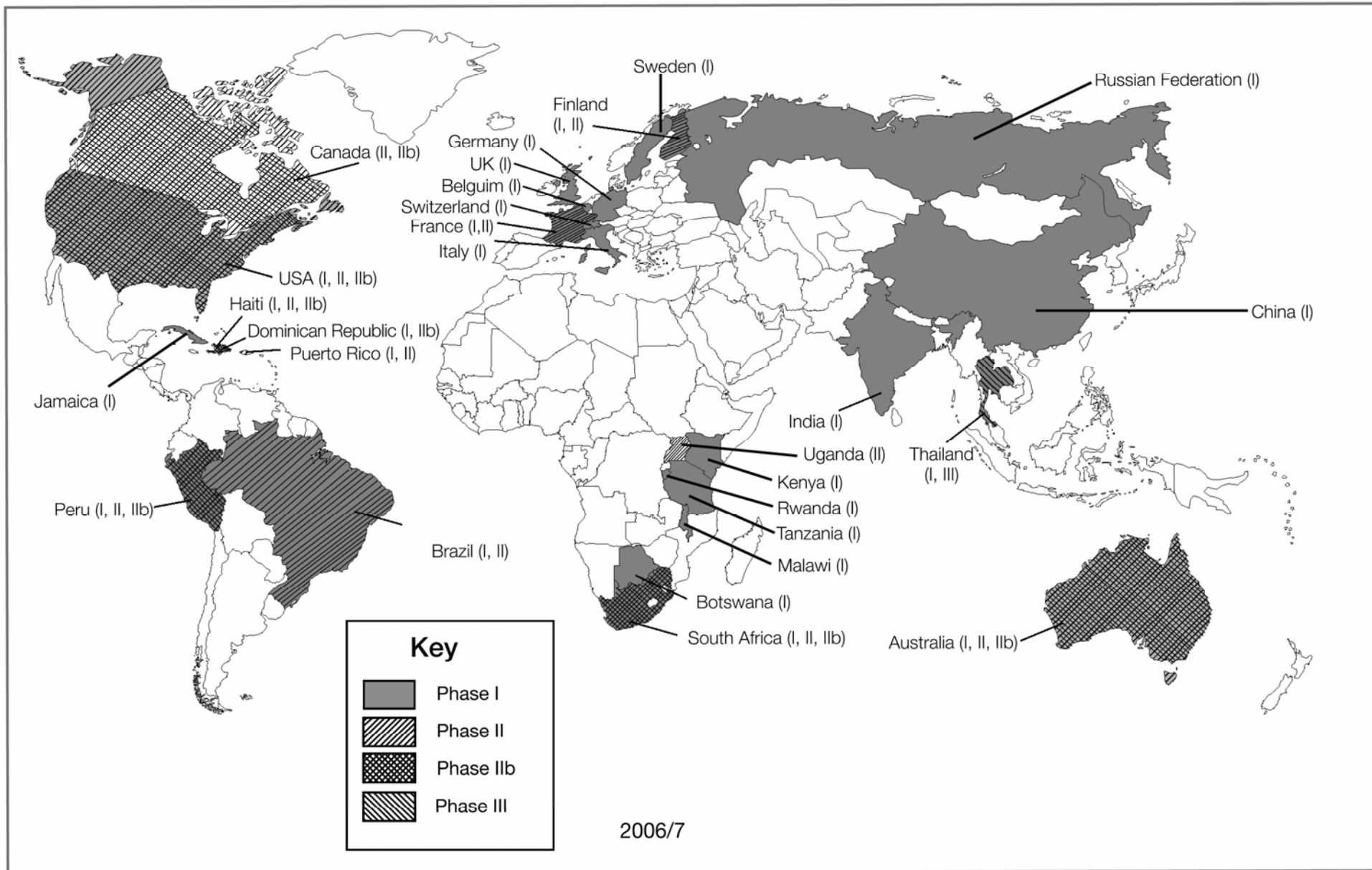
- Researchers collect facts & figures about the community
 - called baseline information:
 - they can compare this to future information collected during the research to see if the research is making an impact.
 - to see if the area is suitable to answer their research question/s
- Also look at practical & logistical information
- Researchers must also consult the community about doing their research as part of a participatory approach (Module 7)



How trial sites are chosen (2)

- Examples of baseline information collected:
 - How many people live there?
 - How many women, how many men?
 - What ages & educational levels?
 - How many people are HIV-positive?
 - How many new HIV infections were there in the past year?
 - Do people want the HIV vaccine to be tested there?
- Examples of practical & logistical information:
 - What is the transport system in the area?
 - Are there any medical, and laboratory facilities there?
 - Are the facilities well maintained?
 - Will they be able to attract enough qualified staff?
 - Are there enough people in the community to meet the trial criteria?

Trials around the world





Where trials are happening around the world?

- Most trials are phase I studies, & are for preventative HIV vaccines
- Important role players in South Africa
 - South African AIDS Vaccine Initiative (SAAVI)
 - Established in 1999 by Government
 - Co-ordinates the development & testing of HIV vaccines in South Africa
 - A lead programme of the South African Medical Research Council (MRC)
 - HIV Vaccine Trials Network (HVTN)
 - International AIDS Vaccine Initiative (IAVI)



HIV vaccine trials in South Africa

- Examples of clinical trials that have, or are happening:
 - Venezuelan Equine Encephalitis (VEE), phase I, started in 2003
 - Replicon vaccine design, preventative trial
 - FIT Biotech's HIV DNA vaccine, phase II, began in February 2006
 - first therapeutic HIV vaccine trial in South Africa
 - Adenovirus (cold virus), phase IIb, began in early 2007
 - Vector vaccine design
 - Called *Phambili* trial
 - Preventative trial

See list of websites in Learner Handbook to keep up to date on the trials