

Clinical Trials in the Developing World

The Issue

Clinical trials are conducted on all new medicines. Regulators will only approve a new medicine if these trials, together with other research data, demonstrate it has a favourable risk benefit profile. The majority of patients recruited into GSK's clinical trials are from Western Europe and the US. Clinical trials are also increasingly conducted in other countries to help develop new medicines more quickly and for certain regulatory and specific scientific reasons. However, the need for clinical research outside Western Europe and the US is questioned by some. They argue that industry is using some of the world's poorest populations as "guinea pigs" for developed world diseases and acting in an unethical way that fails to reflect the standards applied in the developed world. This paper addresses these concerns and sets out the philosophy underpinning GSK's approach to clinical research wherever it is conducted.

GSK's Position

- GSK-sponsored clinical trials world-wide are conducted according to the same fundamental ethical principles. The studies meet international and national regulatory and legislative requirements and follow the research methodologies outlined in the International Conference on Harmonisation (ICH) Good Clinical Practice guidelines. Moreover, GSK-sponsored clinical trials follow the principles contained in the World Medical Association Declaration of Helsinki on the Ethical Principles for Medical Research Involving Human Subjects.
- The majority of GSK's clinical trials are performed in Western Europe and the US. However, we are a global company and while we are committed to maintaining the absolute number of patients we enroll into studies in the US and Western Europe, we are increasing the number of patients we admit from Central and Eastern Europe, Asia and South America to enable medicines to be developed more rapidly. This does not extend to recruiting more patients from Least Developed Countries (as defined by the UN).
- Clinical trials are only conducted in countries where the medicines are likely to be suitable for the wider community. Furthermore, clinical trials of investigational medicines are not conducted in countries when it is known at the outset that there is no intent to pursue registration and make the medicine available for use in that country.
- GSK follows ICH methodologies as a minimum and works, where appropriate, with community leaders, charities, religious figures and Health Authorities, in compliance with local laws and practices, to ensure that trial participants are protected. When necessary, and particularly in the case of developing countries, agreement is also reached, before the start of the trial, on issues such as responsibilities for the standard of care and post-trial treatment.

GLOBAL PUBLIC POLICY ISSUES

GlaxoSmithKline's Position

- The type of reimbursement or other recompense offered by GSK to participate in a clinical trial is appropriate to the local economy and submitted to independent ethics committees for consideration. Similarly, payments to investigators or their institutions is in line with local practices and appropriate to the cultural context.
- Responsibility for post-trial provision of nationally licensed medicines used during a trial lies with governments as part of national healthcare programmes. GSK-sponsored clinical trials will not be carried out unless we are assured at the outset that the healthcare system is able to provide, and is responsible for, the continued care of trial participants. Importantly, where patients are initiated on nationally licensed medicines during a trial for a chronic disease we need to be assured that, where there are no suitable alternatives, these medicines will be made available after the trial to those patients who derived a measurable medical benefit.
- In exceptional circumstances, if these nationally licensed medicines are not funded through the normal healthcare infrastructure, the medicines may be funded by GSK. This commitment is made pending the medicine being made available through the normal healthcare infrastructure or until the patient no longer requires them.
- GSK recognises that there may be circumstances when patients who have derived a measurable medical benefit from a non-approved investigational compound during a clinical trial should continue to receive that compound, even if it has not been approved and licensed for use (eg. the illness being treated is a life threatening illness and there are no alternative treatments). Under such circumstances, post-trial treatment with the investigational compound will be provided with appropriate oversight, for example, in a clinical trial setting.
- Industry has a responsibility to develop well-tolerated and effective medicines. However, responsibility for healthcare delivery lies outside this remit. The issues of access and affordability in developing countries needs to be addressed in partnership through public healthcare systems and a commitment on the part of national governments and the international community to provide health care services, including medicines to the poor.

BACKGROUND

1. Clinical Research Programmes

GSK is increasing the number of patients we recruit into clinical trials from Central and Eastern Europe, Asia and South America (ie. outside the traditional centres of Western Europe and North America) for a number of reasons:

- Clinical trial capabilities in certain other parts of the world have improved to the point that there is simply no reason to maintain a bias in favour of Western Europe and North America. The wider the geographic scope, the faster we can recruit, and the faster we recruit, the sooner we get new medicines to those who need them.

GLOBAL PUBLIC POLICY ISSUES

GlaxoSmithKline's Position

- The overall amount of clinical trial activity in North America and Western Europe in many therapy areas makes it increasingly difficult to find experienced investigators who are able to start trials quickly as well as recruit suitable patients rapidly. Consequently, conducting clinical trials exclusively in these traditional centres would increase development time and so delay approval of new medicines.
- Due to changes in living standards many diseases of the developed world (eg. hypertension, diabetes) are now global diseases. Including patients from all ethnic backgrounds therefore enables GSK to develop global medicines.
- Patients in Central and Eastern Europe, Latin America and parts of Asia have often used fewer medicines compared with those in Western Europe and the US. This makes them good candidates for a clinical trial as it is easier to assess the effect of the products being tested.
- Cost is also a factor, as the recruitment costs per patient in these countries can often be lower.

There are also some specific scientific and regulatory reasons why clinical trials are conducted in developing countries. For example:

- GSK has an ongoing commitment to target diseases that disproportionately affect developing countries, including HIV/AIDS, TB and malaria. When investigational compounds for these diseases enter clinical development, clinical trials in developing countries are usually required. For example, the incidence of malaria in the developed world is too low to design a scientifically robust study to evaluate the efficacy of an investigational compound.
- Clinical trials may be conducted in developing countries in order to assess the relevance and applicability of some therapies within the local system of healthcare (phase IV studies).
- A few developing countries insist on the provision of local clinical trial data as a prerequisite for product registration. For example China, Nigeria, South Korea and India require significant data in local populations. For patients to benefit from GSK medicines GSK-sponsored trials may therefore need to be conducted in these countries. GSK would welcome any efforts to reduce or streamline this requirement and is working in partnership with a number of regulatory authorities to this end.

2. ICH Good Clinical Practice Guidelines

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was established in 1990. It brings together the regulatory authorities of Europe, Japan and the United States, and experts from the pharmaceutical industry via the three regions' trade associations, plus key observers (including the WHO).

GLOBAL PUBLIC POLICY ISSUES

GlaxoSmithKline's Position

The ICH's main purpose is to recommend ways of achieving greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration. Over 45 guidelines on a range of activities have been adopted since the ICH's creation.

All Clinical Trials at GSK are conducted according to the ICH's Good Clinical Practice Guidelines. The Guidelines provide an internationally accepted ethical and scientific quality standard for designing, conducting, recording and reporting trials. They cover issues such as having a clear, scientifically sound protocol, signed by relevant investigators and approved by an Independent Ethics Committee/Institutional Review Board (IEC/IRB); the selection and training of trial investigators; gaining voluntarily-given informed consent from every trial participant; demonstrating that the anticipated benefits justify the risks; and ensuring that the rights, safety and wellbeing of subjects are the most important considerations.

3. Ethical Review of Research Protocols

GSK will always seek formal approval for trials from independent ethics committees. In some developing countries independent ethics committees do not exist or their membership is not in line with regulatory requirements. If an ethics committee does not exist research cannot take place. Where there is a local ethics committee but it does not meet regulatory requirements the study is referred to another ethics committee in another country that meets regulatory requirements. This ensures from a regulatory perspective that GSK holds an approval from a bone fide ethics committee irrespective of the standing of the local ethics committee. Nonetheless, the local ethics committee would still review the study. In the event that it was not in favour of the proposed protocol, that view would take precedence.

GSK is actively working with local regulators and sponsors to develop local capacity in ethical reviews. For example, through our involvement in the global programme - SIDCER (the global Strategic Initiative for Developing Capacity in Ethical Review) and its sub-Group PABIN (Pan African Bioethics INitiative) we are working with other stakeholders on reviewing the ethical environment for clinical trials in developing countries, including issues such as post-study medication, informed consent and training of ethics committees.

4. Informed Consent

GSK recognises the absolute necessity of informed consent and will only ever proceed with a trial once informed consent, in a legally and ethically acceptable form, has been obtained from research participants.

In cultures other than those in Western society, additional measures may often be needed to ensure the objectives of informed consent are met. While still complying with ethical and legal requirements, additional steps are therefore taken to match the objectives of informed consent to local culture. For example local leaders and/or family members may need to be involved.

Where formal *written* informed consent from the participant is not possible in a GSK sponsored trial (due, for example, to poor literacy) investigators will work with independent witnesses. They will formally verify that the purpose of the trial has been explained to the participant and he/she has understood what is proposed and involved.

5. Capacity Building for Biomedical Research

Capacity building can benefit the community by strengthening local research capacity. However, when capacity building is provided, it is important that this does not constitute undue inducement for patients to participate in the study.

Equally, the need for capacity building which is linked to specific clinical trials or programmes can be an important consideration for externally sponsored collaborative research.

Where investigators and/or other institutions do not have the required level of experience or expertise in conducting clinical trials to good clinical practice standards, GSK works with investigators, healthcare professionals and other interested parties to ensure that the necessary ethical and scientific standards are in place. In situations where a reasonable level of specialised equipment is needed to conduct a clinical trial solely sponsored by GSK, it may be provided by GSK and where agreed, left for the use of the investigator or institution. Under these circumstances, the value of the equipment will be included in the Study Agreement as part of the study compensation. Capacity building provided by GSK in the context of a clinical trial occurs on the understanding that it is appropriate to the local environment and is maintained by the local community on completion of the trial.

6. Payments and other Recompense

The type of reimbursement or other recompense offered to patients to participate in a GSK-sponsored clinical trial is appropriate to the local economy and submitted to independent ethics committees for consideration.

At the individual level, reimbursement for costs incurred by the participant are reasonable, and it is particularly important in poorer societies that the individuals do not suffer loss by involvement in a trial. Within some societies it is also important that individuals do not benefit from study involvement to an extent that it sets them apart in that society.

In all circumstances, problems can be avoided by involving the local ethics committee (disclosure of payment plans has been an obligatory part of the ethical review process since the mid-1990s) and ensuring that any payments are appropriate to the local setting. The standard is, and always has been, voluntary participation in clinical trials.

7. Payment to those Conducting a Trial

Payments to investigators for their professional expertise, time and involvement are in line with local practices. These payments embody the concept of "fair market value" so that investigators/institutions are fairly compensated in their local markets for their efforts in conducting good quality clinical trials.

8. Standard of Care

In a research context, the standard of care refers to the nature of the care and treatment provided to participants in research. The standard of care required by study design, and/or offered during a clinical trial will generally be higher than the standard of care that a patient might receive outside a clinical trial. For example, the trial protocol may require more regular assessments of disease progression and patient visits to the clinic.

GLOBAL PUBLIC POLICY ISSUES

GlaxoSmithKline's Position

Conversely, comparator medicines used in a clinical trial could potentially lower the standard of care if it has been established that the treatment the patient would receive outside the clinical trial is likely to be more beneficial. There is much debate relating to the treatments that should be provided to control groups. The debate focuses on whether control groups should receive the “*best current treatment available anywhere in the world*”, or treatment based on an alternative standard of care which takes local circumstances into account, such as the “*best treatment currently available in the country*” in which the research is being conducted. In many circumstances this latter approach will be appropriate as:

- It enables researchers to determine if a new treatment is better than the one currently used in that country. Comparing a new treatment with a treatment that is not used in the local setting will not advance healthcare in that setting as it will not generate data that is considered relevant to the care of patients in that community
- It helps to ensure continued treatment after the trial to the same standard.
- In many disease areas and disease/patient subgroups there is no international consensus on the global best treatment.
- In some cases the best current treatment may be surgery or some other treatment requiring a sophisticated infrastructure or regular monitoring which cannot be provided in developing countries.

For GSK-sponsored clinical trials, any comparators used may not necessarily be identical to those that patients would have received outside the clinical trial provided they can be expected to provide a similar benefit. However, the standard of care required by study design and/or offered during a clinical trial is never less than the local standard of care. In some circumstances the best current treatment available anywhere in the world may be appropriate – for example where there is widespread agreement on the treatment for an infection.

Placebo controlled trials will be conducted where there are compelling and scientifically sound methodological reasons for its use. In all such placebo-controlled studies, GSK will ensure that subjects give their informed consent, without coercion or inducement, that precautions are in place to minimise risks and that there is appropriate oversight by the ethics committees.

9. Post Trial Availability of Medicines

GSK strongly supports the goal of improving access to medicines and we recognise our responsibility for helping to improve access to our products worldwide. GSK is however, concerned by the suggestion that research sponsors should be routinely obliged to provide treatments to participants post-trial.

Investigational (non-approved) Compounds

GSK recognises that there may be circumstances when there is a compelling medical rationale for patients who have derived a measurable medical benefit from an investigational compound during a clinical trial to continue to receive that compound (e.g., the illness being treated is life threatening or seriously debilitating and there are no other treatments available or there are significant risks in switching patients to alternative treatments). When this is the case, post-trial treatment with the investigational compound will be provided with appropriate oversight, for example in a clinical trial setting. GSK commits to provide the investigational compound for as long as necessary or until the compound is approved and licensed in that country.

GLOBAL PUBLIC POLICY ISSUES

GlaxoSmithKline's Position

Nationally Licensed Medicines

GSK is not, in general, responsible for the provision of nationally licensed medicines after a trial. This responsibility lies with governments as part of national healthcare programmes. For this reason, GSK-sponsored clinical trials in chronic conditions will not be carried out unless we are assured at the outset that the healthcare system is able to provide, and is responsible for, the continued care of trial participants. Importantly, where patients are initiated on nationally licensed medicines during a trial in a chronic disease we need to be assured that, where there are no suitable alternatives, these medicines will be made available to those patients who derived a measurable medical benefit after the trial. In exceptional circumstances, if these nationally licensed medicines are not funded through the normal healthcare infrastructure, the medicines may be funded by GSK. This commitment is made pending the medicines being made available through the normal healthcare infrastructure or until the patient no longer requires them.

The issue of post-trial treatment is, where appropriate, addressed in pre-trial agreements, the trial protocol and as part of the informed consent process. Factors to be considered include the disease and the type of medicines used in the study (e.g. preventative, palliative, acute treatment, the availability and affordability of the medicines) and whether post trial access might constitute undue inducement for patients to participate in the study.

10. Treatment Affordability and Access

Industry has a responsibility to develop well-tolerated and effective medicines and it is GSK's intention to make the product available following registration in the markets where the studies are conducted. However, the issues of access and affordability in developing countries need to be addressed through public healthcare systems and a commitment on the part of national governments and the international community to provide health care services, including medicines to the poor. While industry can, and does play a role in this, through offering sustainable preferential prices for key developing world therapies (GSK has, for example, offered preferential pricing arrangements for its vaccines for over 20 years, for ARVs since 1997 and for anti-malarials since 2001) a significant increase in public expenditure is also required.

11. GSK's Research Commitment to address diseases that disproportionately affect the Developing World

GSK has a dedicated vaccines division and a "Diseases of the Developing World" group. We are also one of the world's largest manufacturers of antibiotics and anti-retrovirals with extensive research programmes conducted by other R&D groups. We believe GSK is currently the only company researching both new vaccines and treatments for malaria, tuberculosis and HIV/AIDS - the World Health Organisation's three priority diseases. This research necessarily involves working in partnership with some of the world's poorest communities afflicted by these diseases.

Revised August 2009