

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. Historically, the majority of patients recruited into clinical trials for medicine development have been from Western Europe and the US. However, clinical trials are increasingly recruiting patients from other countries, including developing countries. This shift in focus 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 describes our approach to addressing these concerns and sets out the philosophy underpinning the conduct of GSK clinical research wherever it takes place.

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.
- Historically, the majority of GSK's clinical trials have recruited patients from Western Europe and the US. However, as a global company we are increasing the number of patients we enrol from Central and Eastern Europe, Asia and South America to enable our medicines to be evaluated in broad populations. 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 the risks and benefits for trial participants are effectively evaluated and appropriate measures put in place. 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.
- The type of reimbursement or other recompense offered to trial participants by GSK is appropriate to the local economy and submitted to independent ethics committees for consideration. Similarly, payments to investigators or their institutions reflects fair market value and is in line with local practices and appropriate to the cultural context.

GLOBAL PUBLIC POLICY ISSUES

GlaxoSmithKline's Position

- Responsibility for post-trial provision of nationally licensed medicines used during a trial lies with governments as part of national healthcare programmes. For diseases/conditions that continue beyond the end of an interventional study, GSK-sponsored clinical trials will not be carried out unless we have assurance from the investigator that subjects will receive, or be referred for, any necessary continued healthcare and that the healthcare system is able to provide for the continued care of trial participants.
- In exceptional circumstances, if nationally licensed medicines used during a trial are not funded through the normal healthcare infrastructure post-trial provision of the medicines may be funded by GSK. Such circumstances include those in which individual patients have received measurable medical benefits from nationally licensed medicines during the study and where patients are unlikely to benefit from alternative nationally funded licensed medicines. This commitment is made pending the medicine being made available through the normal healthcare infrastructure or until the patient no longer requires it.
- GSK recognises that there may be circumstances when patients who have derived a measurable medical benefit from a non-approved investigational medicine during a clinical trial should continue to receive that medicine, 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, GSK may extend the study to facilitate appropriate continued access to the investigational medicine. Alternatively, the availability of an expanded access program may serve as a means of continued access.
- Industry has a responsibility to develop well-tolerated and effective medicines; responsibility for healthcare delivery lies outside this remit. The issues of access and affordability in developing countries need to be addressed in partnership through public healthcare systems. This should include a commitment on the part of national governments and the international community (including industry where appropriate) 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 the US) 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 the US. With a wider geographic scope, there are opportunities to reduce the time it takes to develop new medicines as trial recruitment may be faster.
- The overall amount of clinical trial activity in the US and Western Europe in many therapy areas makes it increasingly difficult to find experienced investigators who are able to initiate and recruit patients in a timely fashion. Consequently, conducting clinical trials exclusively in these traditional countries may 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 medicines to be evaluated in broad populations.

GLOBAL PUBLIC POLICY ISSUES

GlaxoSmithKline's Position

- 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 can make them good candidates for a clinical trial as in many circumstances the risks and benefits of the medicines being evaluated can be more readily assessed.
- 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 (often conducted after regulatory approval i.e. 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, Japan, Nigeria, South Korea and India require significant data in local populations. For patients to benefit from GSK medicines, GSK-sponsored trials therefore need to be conducted in these countries. GSK would welcome any efforts by these regulatory authorities to harmonise or streamline their requirements to help ensure that clinical data can be generated in the most expedient way.

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 US, and experts from the pharmaceutical industry via the three regions' trade associations, plus key observers (including the WHO).

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 international regulatory requirements. If a local ethics committee does not exist, GSK will not conduct the trial. Where there is a local ethics committee but it does not meet international regulatory requirements the study is also overseen by another ethics committee in another country that meets international regulatory requirements. This ensures from a regulatory perspective that GSK holds an approval from a regulatory-compliant 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.

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 to document a verbal consent process. 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.

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 will work 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 is reasonable, and in poorer societies it is particularly important 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.

GLOBAL PUBLIC POLICY ISSUES

GlaxoSmithKline's Position

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. Care is therefore taken to avoid undue financial influence on participants' decisions.

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.

GSK is committed to disclosing all research payments made to healthcare professionals and their institutions involved in GSK-sponsored clinical trials. This process began in late March 2011 with disclosure of payments made to US healthcare professionals and their institutions for research studies that began from January 2010 onwards. It captures payments for all phases of medicine discovery and development, including clinical trials. Outside the US, we will continue to work towards disclosure of payments. To this end, we will disclose payments to healthcare professionals and their research institutions on an aggregate basis, commencing with the publication in 2013 of payments made during 2012.

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 often 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.

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 may be appropriate because:

- In many disease areas and disease/patient subgroups there is no international consensus on the best global treatment.
- 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 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.

GLOBAL PUBLIC POLICY ISSUES

GlaxoSmithKline's Position

Placebo controlled studies are conducted only when there are compelling and scientifically sound methodological reasons, where the risks to the patients who receive the placebo are minimized, where the studies are reasonable in relation to the knowledge gained, and when patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

As for all studies, GSK will ensure that subjects in placebo-controlled studies 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, GSK may extend a study to facilitate appropriate continued access to the investigational product. Alternatively, the availability of an expanded access program may serve as a means of continued access.

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 by the investigator that subjects will receive or be referred for any necessary continued healthcare and that the healthcare system is able to provide for the continued care of study subjects.

In exceptional circumstances, if nationally licensed medicines used during a trial are not funded through the normal healthcare infrastructure, post trial provision of the medicines may be funded by GSK. Such circumstances include those in which individual patients have received measurable medical benefits from nationally licensed medicines during the study and where patients are unlikely to benefit from alternative nationally funded licensed medicines. This commitment is made pending the medicine being made available through the normal healthcare infrastructure or until the patient no longer requires it.

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 medicine 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 long-standing commitment to research and development into diseases of the developing world (DDW). Our R&D portfolio includes projects for a number of diseases of particular relevance to developing countries including: bacterial meningitis, Chagas disease, chlamydia, dengue fever, HIV/AIDS, human African trypanosomiasis, leishmaniasis, malaria, pandemic flu, pneumococcal disease and TB.

We are keen to do more but we recognise that the challenges are too complex to be addressed by any one organisation alone. Partnership is essential and that is why we are pursuing an 'open innovation' approach to DDW research, working together with industry, academia, NGOs and governments.

Open innovation at GSK includes:

- Sharing our expertise and resources with scientists from around the world through our Tres Cantos Open Lab.
- Sharing our intellectual property and know-how through the Pool for Open Innovation against Neglected Tropical Diseases.
- Being more open with our data and DDW research to help stimulate research outside GSK.

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