GSK Public policy positions

Public Disclosure of Clinical Research

The Issue

Pharmaceutical companies are legally required to disclose relevant data from clinical trials and other research to the appropriate national or regional regulatory authorities as part of the medicine development and approval process. After approval, companies have a continuing obligation to provide regulatory authorities with updated safety information from clinical research and other sources. This ensures regulators can accurately assess the efficacy of medicines and monitor their safety. Safety and efficacy information is also provided to healthcare professionals through prescribing information which is approved by regulators.

In addition to fulfilling these regulatory requirements, the pharmaceutical industry also communicates the results of its clinical research by publishing in scientific journals; by presenting results at scientific congresses; and, in line with evolving legal requirements and established industry commitments, by posting information and results on internet-based public registers and databases.

Despite this, however, concerns have been raised by some about:

– whether study results which may be viewed as “negative” for companies’ medicines are published in scientific literature;
– whether published studies accurately reflect the conduct of the study;
– the extent to which those wishing to examine, replicate, challenge or combine the results provided on registers and in publications with other studies in meta-analyses, are limited by the level of data posted; and
– whether some journal articles are “ghost-written” (whereby doctors put their name to articles written by pharmaceutical companies).

This paper outlines GSK’s approach to addressing these issues in the public disclosure of the results from our clinical research.

GSK’s Position

– When studies are initiated, protocol summaries of GSK studies are posted on internet registers [e.g. http://www.clinicaltrials.gov/ and https://www.clinicaltrialsregister.eu/] and/or our own register [http://www.gsk-clinicalstudyregister.com/]. Following their completion result summaries are also posted - irrespective of the outcome of the study.

– This commitment includes all our clinical trials (phase I-IV) as well as our observational studies and meta-analyses that evaluate our medicines. It also includes posting results from studies of terminated compounds in order to help inform the scientific community about non-productive areas of research and to reduce unnecessary exposure of study participants to similar compounds in other clinical trials.

– GSK’s disclosure policy goes beyond what is required by laws and regulations. For example, our commitment to post on our register phase I studies, observational studies and meta-analyses that evaluate our medicines, goes beyond what is required by regulations in the US and EU.

– We consider these postings on the internet to be supplementary to, and not a replacement for, the need to publish studies in peer reviewed journals. We submit the studies described above as more comprehensive manuscripts for publication in peer reviewed journals that are indexed by online search engines. This approach goes beyond the existing industry–wide (IFPMA) obligation on companies to submit all Phase 3 results and others of significant medical importance for publication. Where GSK studies are not published, we provide study conclusions on our own Clinical Study Register.

– Since 2011, public disclosure of result summaries takes place within specified periods of time from the completion of GSK studies. In other words, we will not wait until approval or termination of the medicine before posting result summaries or submitting manuscripts to peer reviewed journals. Our approach is to post result summaries within 8-12 months (for pharmaceuticals) and within 18-24 months (for vaccines) of the completion of studies and to submit a manuscript to a peer reviewed journal within 18-24 months.

- For newly-initiated late phase studies, when trial results are published as manuscripts in the scientific literature we also post the full protocol on our Clinical Study Register so that interested parties can review the details of how the study was conducted.

- In February 2013 GSK announced plans to make our Clinical Study Reports (CSRs) publicly available through our Clinical Trials Register. CSRs are formal study reports that provide more details on the design, methods and results of clinical trials and form the basis of submissions to the US FDA, EMA and other regulatory agencies.

- This commitment relates to CSRs for clinical studies for all of GSK medicines going forward once the medicine has been approved or terminated from development and the results have been published as manuscripts in the scientific literature. Patient data in the CSRs and appendices with patient data listings will be removed to ensure that patient confidentiality is maintained. Notwithstanding this CSR commitment, GSK will continue to post result summaries on our Clinical Trials Register.

- In addition, GSK intends to post CSRs for all outcome studies (phase IIb and beyond) for approved medicines dating back to the formation of the company in 2000. This will require retrieval and examination of each historic CSR to remove personally identifiable information. Given the significant volume of studies involved, we have put in place a dedicated team to conduct this work which we expect to complete over a number of years. Posting will take place in a step-wise manner, with priority given to CSRs for our most commonly prescribed medicines.

- In May 2013 GSK launched a new online system on gsk.com [https://clinicalstudydata.gsk.com/] enabling researchers to request access to anonymised patient level data from GSK sponsored clinical trials. Trials are listed on the system once the medicine studied has been approved or terminated from development and the study has been accepted for publication.

- In late 2013 the GSK site was re-configured into a multi-sponsor request site https://www.clinicalstudydatarequest.com/ to include studies conducted by other sponsors. Other clinical trial sponsors and funders are invited to list studies on the site with the aim of transitioning it to a broader fully independent system. We hope that such a system will be in place as soon as possible.

- The names of the investigators who participate in our clinical studies that were initiated on or after January 2009 are available on our Clinical Study Register.

- Since January 2010 GSK has disclosed the payments we make to US healthcare professionals and their institutions for research studies. Outside the US, we are working towards a similar level of disclosure, initially at the aggregate level but moving to the individual level over time.

- GSK's policy prohibits "ghost writing" of journal manuscripts and abstracts by requiring authorship and acknowledgements for scientific publications consistent with the requirements of the International Committee of Medical Journal Editors (ICMJE). GSK and external medical writers are either named as authors or included in the acknowledgement section of manuscripts.

Background

The Clinical Development Process

Evaluation of an "Investigational Medicinal Product" (IMP) or "Investigational Vaccine" (IV) is done through trials and is usually conducted in four main phases. Each phase addresses different questions that determine if the testing of the IMP or IV can proceed to the next phase.

Phase I: Phase I studies are primarily concerned with assessing the investigational product's safety usually in a small number of healthy human volunteers (typically between 20 and 100 people) and are designed to determine what happens to the IMP or IV in the human body.

Phase II: An investigational product that passes the Phase I testing hurdle then moves on to Phase II, which usually includes the "proof of concept" stage. Here for the first time, it is generally administered to carefully

selected patients suffering from the disease which the product will potentially treat. Generally 100 – 300 patients are enrolled in these Phase II studies. Prophylactic vaccine trials enroll up to several hundred healthy volunteers. Therapeutic vaccine trials enrol volunteers who are already infected or have the disease.

The aim of the studies is to determine if the investigational medicine addresses the illness it is intended for, as well as the amount and frequency of dosing necessary to achieve the optimal benefits for patients with the fewest side effects.

Phase III: In Phase III studies, the investigational product is given to hundreds and frequently thousands of patients. Phase III studies require differing periods of time to complete, depending on the disease being studied. Anti-infective studies can be conducted relatively fast; but Phase III studies in chronic diseases and for vaccines may require years.

Phase IV: Trials of a medicine or a vaccine may continue after it has been approved for marketing. Known as Phase IV trials, they may further evaluate the effect of the medicine or vaccine for the approved use, assess other potential uses, or yield additional safety data. Regulatory agencies may require these trials to address specific questions.

Other types of clinical research, such as, **observational research** (using data collected during the provision of routine healthcare) and **analyses** of data that is combined from a number of clinical trials (e.g. meta-analyses), are increasingly seen as important evidence in the evaluation of the risks and benefits of medicines.

GSK & Clinical Research Data

The guiding principle for GSK is to disclose publicly the results of GSK-sponsored clinical research that evaluates our medicines, irrespective of whether the results are likely to be perceived as positive or negative. Likewise, GSK encourages investigator sponsored studies supported by GSK to conduct and publicly disclose research consistent with GSK Policies, as well.

Internet-based Registration of Ongoing Clinical Trials

Publicly available internet-based registration of ongoing clinical research can provide a stimulus for increased participation. It also provides an important reference point so interested parties can track the subsequent public disclosure of the results.

We post protocol summaries of all GSK-sponsored clinical trials (phase I-IV) of investigational and marketed medicines on external/national registries [such as http://www.clinicaltrials.gov/] as required by laws and regulations and on GSK's own Clinical Study Register [http://www.gsk-clinicalstudyregister.com/] before the first subject is enrolled. We also post protocol summaries for other clinical research that evaluates our medicines, namely, observational research and pooled analyses/meta-analyses of our clinical trials on the GSK Clinical Study Register.

Publication and Internet-based Posting of Clinical Research Results

Traditionally, research results have been publicly disclosed by seeking to publish studies in peer reviewed scientific literature; however, there are well recognised constraints associated with this approach. With limited journal capacity, some studies or analyses may not be considered a priority by some journals, and therefore may not be accepted for publication.

Posting result summaries on internet-based registers is part of a solution as it ensures that the results of clinical studies are available in the public domain whether or not they are accepted for publication. GSK was the first company to launch an internet-based clinical study register http://www.gsk-clinicalstudyregister.com/which focussed on providing result summaries from all our clinical trials (phase I-IV) of marketed medicines irrespective of the study outcome.

Regulatory requirements to disclose research results have since arisen and public registers [e.g. http://www.clinicaltrials.gov/] have been established to serve as repositories for this information. GSK however believes it is important that the results of all types of clinical research that evaluate our medicines are disclosed. In January 2009, we therefore extended our commitment to include all our observational studies and meta-analyses that evaluate our medicines on our Register. We also recognise that information from terminated research programmes can help inform the scientific community on the most productive areas of research to progress and help to reduce unnecessary exposure of study participants to similar compounds in other clinical trials. We furthered our disclosure commitment in January 2009, by extending our disclosure to include all studies of terminated compounds. This approach to observational study data and meta-analyses, as well as to studies of terminated compounds, goes beyond the majority of regulatory requirements in countries where we conduct trials.

In GSK's view, posting result summaries should be seen as supplementary to and not a replacement for, the need to publish studies in peer reviewed journals. We therefore seek to submit our clinical research results of our medicines as more comprehensive manuscripts in peer reviewed journals. Where possible, we also want to enable researchers and medical practitioners to retrieve the published paper using search engines such as Medline and Embase. Our approach is therefore to submit manuscripts to journals that are indexed by online search engines.

Where studies are not published we will provide study conclusions on the GSK Clinical Study Register.

Where the sponsor of these studies is not GSK, for example, where we support a study by providing GSK product, external researchers are encouraged (via written agreements) to post protocol and result summaries on internet-based registers and submit the results for publication in a searchable peer-reviewed journal.

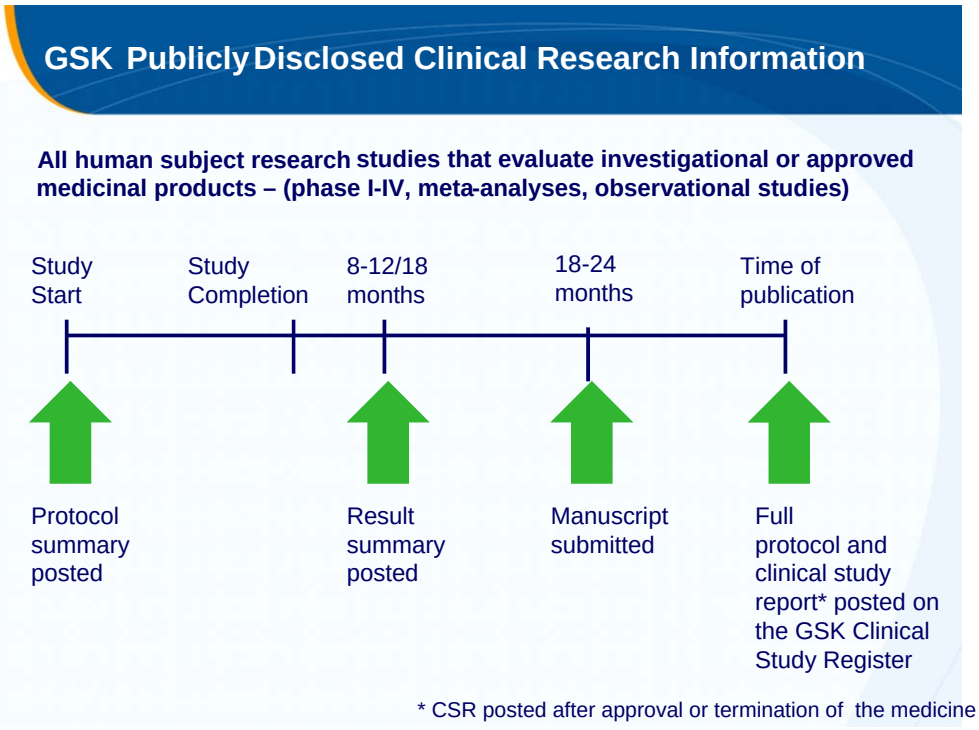
Timing

Historically our approach to posting result summaries and seeking publication of studies in journals has been linked with the time of medicine approval or decision to terminate further development of the medicine.

In July 2011 we modified our approach and decided to adopt one in which public disclosure of results takes place within specified periods of time from the completion of our studies. In other words, we will not wait until approval or termination of the medicine before posting results summaries or submitting manuscripts to peer reviewed journals. Our approach is to post result summaries within 8-12/18 months of the completion of studies and to submit a manuscript to a peer reviewed journal within 18-24 months.

In addition, for newly-initiated late phase studies when results are published as manuscripts in the scientific literature we will post the full protocol on our Clinical Study Register so that interested parties can review the details of how the study was conducted.

Since December 2013, Clinical Study Reports (CSRs) are publicly available through our Clinical Trials Register. This commitment relates to CSRs for clinical studies of all of GSK medicines once the medicine has been approved or terminated from development and the study has been published as a manuscript in the scientific literature. Patient data in the CSRs and appendices with patient data listings is removed to ensure that patient confidentiality is maintained. Access can be requested via the clinical trial request site https://www.clinicalstudydatarequest.com/.



Authorship

Authorship and acknowledgements for manuscripts follow ICMJE criteria and are determined based on the level of contribution to study design, data acquisition, analysis and interpretation, and writing or revising the manuscript. Some journals however, have a more narrow definition of authorship and this convention is followed for such journals.

The named primary author for a paper must actively participate in the drafting process and lead the content development of manuscripts. The primary author works closely with co-authors and retains final approval authority for the manuscript. Any GSK staff or contractors such as professional medical writers who contribute to the development of manuscripts for external authors (e.g. assistance in assembling initial drafts, tables and figures, collating co-author comments and revising the document based on author input) are named in the article either as authors when their contribution meets authorship criteria or by description of their contribution within the acknowledgements section.

To inform investigators of the outcome of a GSK-sponsored trial and to help ensure that the results are submitted for publication in a timely manner, GSK will provide investigators with a summary of the overall trial results and, if required to support planned publications, will provide relevant reports, figures or tables. GSK honours reasonable requests to allow investigators to review the complete study database at a GSK site or other mutually agreeable location.

To help ensure that clinical study results are reported in an objective, accurate and balanced manner, GSK reviews proposed manuscripts prior to submission. While GSK does not suppress or veto submission of manuscripts, the timing of submissions may need to be delayed to allow GSK the opportunity to seek necessary intellectual property protection.

GSK generally does not support publication of single centre data derived from a multi-centre trial. It is GSK's position that the results from the entire trial should be published before information from individual centres is published and that individual centre data should always reference the primary publication of the entire study.

Access to Patient Level Data

Publication of clinical studies in the scientific literature and result summaries on registers typically only contain summarised data. These summaries therefore have limitations for those who wish to examine the data more closely or to combine it with other studies in meta-analyses. To address these limitations, there needs to be greater access to underlying patient level data. In May 2013, we therefore established an online system whereby researchers can request, via a GSK website, access to anonymised patient level data from GSK sponsored clinical trials.

Clinical studies of authorised medicines in approved indications (anywhere in the world) and medicines terminated from development are listed on the website once the primary manuscript for the study has been accepted for publication. Studies that have not been accepted for publication and are no longer being progressed will also be available, as will be studies of approved medicines in indications that are terminated from development.

All GSK studies (including those conducted solely in a *specific* country or *region* such as Europe or Asia) initiated after 1 January 2013 will be added to the website as they progress and meet the above criteria for inclusion. We are also including globally conducted clinical studies (phase I-IV) started since 2000. This retrospective listing of studies will be complete in 2015.

Anonymised patient level data will be made available from studies on the GSK website provided that an Independent Review Panel approves an associated research proposal and the investigator signs a Data Sharing Agreement. The Independent Review Panel comprises external experts. It accepts or rejects proposals based on the scientific rationale and relevance to medical science or patient care. The panel also considers the qualifications of the investigators and the management of potential conflicts of interest.

Access to the data is provided in a secure, password protected internet environment which has controls in place to prevent data being downloaded or transferred. Analytical software is provided so that researchers can combine data, conduct analyses and download the results. The Data Sharing Agreements will help ensure the data are used solely for the agreed research purpose.

Together with other sponsors of clinical trials, GSK is encouraging a broader independent system for sharing clinical trial data with external researchers that would enhance accessibility to more clinical trial data, allow researchers to combine data from multiple sponsors, industry and non-industry, and help ensure that the contribution of study volunteers to medical innovation is fully realised.

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