Cancer Research UK response to House of Commons Science and Technology committee clinical trials inquiry
February 2013

1. Every year around 300,000 people are diagnosed with cancer in the UK. Every year more than 150,000 people die from cancer. Cancer Research UK is the world’s leading cancer charity dedicated to saving lives through research. Together with our partners and supporters, Cancer Research UK’s vision is to bring forward the day when all cancers are cured. We support research into all aspects of cancer through the work of over 4,000 scientists, doctors and nurses. In 2011/12 we spent £332 million on research. The charity’s pioneering work has been at the heart of the progress that has already seen survival rates in the UK double in the last forty years. We receive no government funding for our research.

2. Clinical studies are a vital strand of the work Cancer Research UK undertakes to bring forward the day all cancers are cured. We currently fund over 240 clinical studies in the UK; we are one of the largest funders of clinical research in Europe. In 2011/12 over 37,000 patients were recruited to clinical studies supported by CR-UK.

3. We take an active role in ensuring that regulation associated with clinical studies is proportionate to allow patients to participate and benefit from the results of clinical research. In February 2012, together with the Academy of Medical Sciences, Cancer Research UK brought together leading figures from across the health research sector to discuss the evolving regulatory landscape. Cancer Research UK has also led on coordinating a joint statement, between academia and industry funders, to feed into revisions of the EU Clinical Trials Directive.

We would therefore welcome the opportunity to provide oral evidence to the committee.

Our key points are as follows:

- Cancer Research UK is broadly supportive of the draft Clinical Trials Regulation and its aim to streamline and improve the regulatory environment for clinical trials of investigational medicinal products in Europe. We believe that certain aspects of the Regulation could be amended further in order to facilitate more effective running of clinical trials in the UK.
- The Health Research Authority (HRA) has already demonstrated its competency in regulating research in the UK.
- We are particularly pleased that in October 2012 the HRA announced a feasibility study to test the potential benefits of a simplified and streamlined HRA assessment for all research in the UK.

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1 Transforming the regulation and governance of health research in the UK. May 2012 http://www.cancerresearchuk.org/prod_consump/groups/cr_common/@nre/@pol/documents/publication/cr_087422.pdf
2 Proposal for an EU Regulation on Clinical Trials: A joint statement from non-commercial and commercial organisations, December 2012 http://prodcontrib.cancerresearchuk.org/cancer-info/publicpolicy/workingwithgovernment/europe/ssLINK/CTRJOINTSTATEMENT
NHS. This feasibility study should remain a key focus for the HRA; as if successful it has the potential to significantly impact on the environment for running clinical studies in the UK.

- Cancer Research UK welcomes efforts to improve transparency in research, especially the publication of negative data from all sectors involved in clinical studies.
- We would support requirements for clinical studies to publish a summary of results within a year of when the data analysis is planned in their protocol, which is submitted as part of regulatory approval to set up a clinical study.
- Solutions to increase transparency must be discussed and implemented at an international level in order to improve standards for studies and benefit patients. Without these key discussions it is possible that isolated action at either the UK or EU level could further discourage clinical research from being located in Europe, without benefitting patients.

4. We have used the term ‘clinical study’ when referring to all types of clinical research undertaken in the NHS in the UK. We use the specific term ‘clinical trial’ only when referring to a clinical trial of an investigational medicinal product, which is currently regulated by the EU Clinical Trials Directive.
   The term ‘clinical study’ encompasses ‘clinical trials’ and studies that look at other interventions such as screening tests.

1. Do the European Commission’s proposed revisions to the Clinical Trials Directive address the main barriers to conducting clinical trials in the UK and EU?

5. The EU Clinical Trials Directive 2001/20/EC (CTD) set out with the best intentions to improve the regulatory landscape and the quality and safety of clinical trials in Europe. However it has been widely acknowledged that the CTD contributed to the general trend of decreasing numbers of clinical trials in Europe without providing benefits to patients. Research conducted by Cancer Research UK at the time found that “CTD had resulted in a doubling of the cost of running non-commercial cancer clinical trials in the UK and a delay to the start of trials” and research staff were “unable or unwilling to open trials in non-UK centres because of the different interpretation of the CTD by member states.”\(^3\) Between 2003 (before the Directive) and 2007 (following the Directive) the time to set up a study increased by 65% and the staffing requirements increased by 75%.

6. Cancer Research UK is broadly supportive of the draft Regulation adopted by the European Commission on 17 July 2012 and its aim to streamline and improve the regulatory environment for clinical trials of investigational medicinal products in Europe. Our assessment, based on consultation with our Clinical Trials Units, is as follows:

• As a Regulation this legislation will achieve one of its principal goals in harmonising the regulatory system for clinical trials across Europe.
• Provisions in the new Regulation will improve the set-up and running of multinational trials. For example, we welcome the legislation’s explicit introduction of co-sponsorship as well as the introduction of a single European portal for applications.
• Cancer Research UK’s main concern is how the Regulation will work in practice. Provisions such as the single European application portal have the potential to greatly improve the application process and reduce trial set up times. However we have requested more information to understand how the new systems will operate and what resources will be allocated to it.
• The Regulation has introduced a risk adapted approach. This means that the levels of monitoring and reporting associated with a trial are adapted to suit the level of knowledge about a medicine being tested. For example a medicine which is being used within its existing licence would require less assessment compared to a treatment being tried in man for the first time. We welcome this move as the previous ‘one size fits all’ approach meant that many academic trials had a disproportionate amount of regulatory oversight.
• Set timelines for approvals have been introduced into the legislation which should provide a marked improvement over existing timelines in some member states.

7. We believe that certain aspects of the Regulation could be amended further in order to facilitate more effective running of clinical trials in the UK. We have put forward amendments to both the Medicines and Healthcare products Regulatory Agency (MHRA) and the European Parliament:

• To reduce the scope of the Regulation so that clinical studies which require additional monitoring but do not pose any additional risk to patients would not fall under the Regulation.
• To ensure that only medicinal products fall within the scope of the Regulation.
• To clarify language around the terms clinical trial and clinical study.
• To risk adapt the safety reporting mechanisms so that treatments which are considered standard use do not need to submit particular types of safety reporting.

8. The purpose of these amendments is to improve the efficiency of running clinical trials and make the Regulation proportionate to the type of work being conducted by academic researchers.

9. If clinical trials cannot take place due to excessive regulatory requirements then no patient benefit can be derived at all. Amendments to the proposed Regulation must be carefully considered to make sure they do not have the same unintended consequences.

2. What is the role of the Health Research Authority (HRA) in relation to clinical trials and how effective has it been to date?

10. Clinical studies do not solely involve the testing of a medicine; many studies involve testing new devices, non-medicinal products and surgical interventions. The Health Research Authority has responsibility for regulating and approving many elements of clinical studies, however many important regulatory requirements sit with other bodies such as the MHRA.
11. The Health Research Authority’s role in relation to clinical studies is through the approval of the ethical aspects undertaken by National Research Ethics Service.

12. The Health Research Authority’s current role in relation to clinical studies is through the approval of the ethical aspects undertaken by National Research Ethics Service. Since its formation in December 2011, the HRA has demonstrated its competency in regulating research in the UK. It has also shown that it is capable of leading a programme of work to streamline and improve regulation and governance of clinical research in the UK. We are particularly pleased that in October 2012 the HRA announced a feasibility study to test the potential benefits of a simplified and streamlined HRA assessment for all research in the NHS. In our evidence to the Academy of Medical Sciences review of regulation and governance of health research in June 2010 we outlined that the biggest barrier facing clinical studies in the UK was the layers of governance associated with seeking permission from NHS Trusts to run studies. Our main recommendation was to develop a streamlined process for these NHS permissions, to be implemented at a national level. We strongly believe that the feasibility study being run by the HRA is the biggest step towards achieving this recommendation, with the ultimate vision outlined as:

13. ‘NHS organisations would be able to rely on the HRA assurance and devote their review to confirming their capacity and capability to host and deliver the research. RECs would be able to focus their expertise on projects raising ethical issues.’

14. To our knowledge there has not yet been data published outlining the impact of the HRA, however we remain confident that its establishment has been one of the most important breakthroughs in the regulation of UK clinical research. Our priority is that the HRA is able to continue to focus on developing a streamlined assessment. The draft Care and Social Support Bill currently passing through pre-legislative scrutiny will grant the HRA statutory footing and allow it to continue to develop independently from Government, and push forward with its programme of work.

4. How could the occurrence and results of clinical trials be made more open to scrutiny? Who should be responsible?

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* Cancer Research UK submission to the Academy of Medical Sciences review of the regulation and governance of medical research. June 2010
  [http://www.cancerresearchuk.org/prod_consump/groups/cr_common/@nre/@pol/documents/generalcontent/cr_053410.pdf](http://www.cancerresearchuk.org/prod_consump/groups/cr_common/@nre/@pol/documents/generalcontent/cr_053410.pdf)
15. Cancer Research UK welcomes efforts to improve transparency in research, especially the publication of negative data from all sectors involved in clinical studies, and supports the AllTrials campaign.6

16. Over the past 10 years Cancer Research UK has financed and endorsed 298 trials of more established treatments (late phase trials) organised by hospital trusts or universities and now completed. Of these, 183 have reported results to date and the remaining 115 trials have yet to be fully analysed. One of the reasons for this is that a trial cannot generally report until a pre-defined time point has been reached or a specified number of events have occurred. See appendix for a case study.

Results of clinical studies

17. Transparency is an important principle in research studies, from basic research through to clinical studies regardless of whether supported by academia or industry. We welcome efforts to improve transparency in research, especially the publication of negative data from all sectors involved in clinical studies. For example, we are involved in initiatives that take on drugs to further their development and publication of previous trial data on these compounds would speed up progress and reduce unnecessary duplication effort.

18. Cancer Research UK has policies in place to support transparency in research studies. We require that trials funded through our Clinical Trials Awards and Advisory Committee undertake clinical trial registration and we monitor when these trials publish their results. Cancer Research UK runs the CancerHelp UK clinical trials database which aims to list all cancer studies recruiting in the UK - not just those supported by Cancer Research UK.7

19. CancerHelp UK works with trial teams to produce summaries of studies to provide useful, easily understandable information for the public. This helps patients with cancer identify which studies they could potentially participate in as well as giving information on both positive and negative studies that have been completed. The database currently includes details of approximately 500 studies recruiting people in UK, and more than 400 summaries of study results. In 2012 we added 83 results summaries, including 25 from studies that had received funding from Cancer Research UK and 15 that were sponsored by pharmaceutical companies.

20. We would support requirements for clinical studies to publish a summary of results within a year of when the data analysis is planned in their protocol, which is submitted as part of regulatory approval to set up a clinical study. It should be noted however that the planned analysis could be many years after recruitment to the study has ceased. Timings of analyses are not generally scheduled in terms of months and years but instead are event-driven. If a summary of results is not available within a year of the planned analysis then an explanation should be provided and

6 http://www.alltrials.net/supporters/cancer-research-uk/
7 http://www.cancerresearchuk.org/cancer-help/trials/
publicly available. It may also be necessary to build in an annual reporting mechanism for studies that fail to report in a year, to ensure there is continued pressure to publish.

Patient level data

21. We believe that the issue of releasing patient level data is separate to that of releasing the summary of results from a clinical study.

22. There are important issues relating to patient consent and confidentiality to take into account when considering transparency of clinical studies data beyond the publication of summary results.

23. Requests to access patient level data from clinical studies need to be considered very carefully. We support the responsible sharing of patient level data, with investigators who have set out clear plans for how they will interrogate data through peer-reviewed studies.

24. On the issue of patient level data, the need for transparency must be balanced against the following concerns:

   • patient consent and confidentiality; patients may have only provided consent for their data to be used in a certain way; any measure to promote transparency would need to respect this historic consent
   • the risks that information could be misrepresented which could undermine public understanding of a treatment or research finding;
   • maximising usefulness and minimising risks by balancing the level of detail in the data (e.g. aggregated findings versus patient level data) with how widely these data are shared (e.g. publicly available versus controlled access); and
   • the need to ensure the environment incentivises the funding and delivery of clinical studies, for example by granting a researchers a period of exclusivity for the use of their data.

25. It is important to ensure that full consideration has been given to ensuring solutions work across the range of clinical studies, not just trials of investigative medicinal products (currently covered by the EU Clinical Trials Directive).

26. This is a complex area so it is important that any action the Government takes is well thought through, aligns with actions taken at an international level, and doesn’t inadvertently affect the ability to conduct research that will benefit patients.

Ethics

27. Ethics committees (which the HRA oversees in the UK) have a significant role in upholding the transparency of study data and other ethical concerns about missing data.

28. The Declaration of Helsinki makes it clear that the:
“Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports.”

29. This is a guideline that should be upheld by ethics committees and deliberated upon when a study is being considered for approval. Many of the concerns raised on the issue of data transparency for clinical studies could conceivably fall within the remit of ethics committees as it their role to ensure the ethical conduct of research studies as well as ensuring the results of the study being used to advance medical knowledge.

30. We welcome that the Health Research Authority will be piloting a scheme which will determine whether or not it is feasible for ethics committees to ascertain whether researchers have not published their previous research projects. It will be important that this extra check will not extend the time it takes to gain ethics approvals. The community should be consulted on what ethics committees would constitute appropriate and robust assurance from Sponsors and researchers. We therefore look forward to engaging further with the HRA as their pilot develops.

31. Cancer Research UK would not support a system where ethics committees automatically refused study approval to researchers based on failure to publish previous work. We believe such a system has the potential to be onerous and ineffective. The time taken for ethics committees to conduct comprehensive analysis of the principle investigator, investigational team, Sponsor or even on an IMP would cause severe delays in research without greatly supporting better transparency practices. In practice, researchers and Sponsors who wished to avoid publication would not be coerced by this rule, and it would simply add complexity to applications and the timelines for ethics approvals.

Clinical Trials Regulation

32. The draft Clinical Trials Regulation (as proposed in July 2012 and not taking into account any proposed amendments) supports greater transparency than exists under the current Clinical Trials Directive:

- Article 78 of the current draft of the Clinical Trials Regulation states that a new database will capture all information relating to clinical trials in Europe and makes it compulsory for this to be made public while protecting patient and commercial confidentiality.
- Article 33 also makes requirements for Sponsors to notify regulators of the start and end of the trial.
- Article 34 (3) states that “within one year from the end of a clinical trial the sponsor shall submit to the EU database a summary of the results of the clinical trials” with the exception that results can be delayed when scientifically justified.

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8 World Medical Association, Declaration of Helsinki, Article 30
33. We view these as useful steps towards ensuring that all trials are registered and therefore can be followed up to ensure that the results have been published. While definitions could be clearer on the exact nature of the data that would be published and what exactly the legislation could define as commercially confidential, the Regulation does appear to give legislative backing to support a greater level of transparency than existed under the Directive.

5. Can lessons about transparency and disclosure of clinical data be learned from other countries?

34. The push for transparency must also involve the international research community if it is to be successful. Solutions to increase transparency must be discussed and implemented at an international level in order to improve standards for studies and benefit patients. Without these key discussions it is possible that isolated action at either the UK or EU level could further discourage clinical research from being located in Europe, without benefitting patients. Discussion with the US in particular should be encouraged due to its size and the influence the American market has on the global pharmaceutical industry.

We would be happy to provide any further information or an expert to discuss these issues further, as required. Please contact Dan Bridge on Daniel.bridge@cancer.org.uk or telephone 0203 469 8153.
Appendix

Case study: Intercontinental trial

Intercontinental was a trial looking at intermittent versus continuous hormone therapy for prostate cancer that had continued to grow but had not spread - it was an international trial supported by Cancer Research UK.9

Doctors thought that hormone therapy given intermittently rather than continuously may work just as well and may also reduce side effects. The main aims of this trial were to compare intermittent and continuous hormone therapy to see the difference between how long the men lived and how it affected their quality of life.

Recruitment of patients:
- Sample size - 1,386
- Start 01/10/2002
- End 30/11/2005
- Publication date (N Engl j med 367;10 nejm.org September 6, 2012)

The Independent Data and Safety Monitoring Committee recommended halting the trial after a planned interim analysis demonstrated that a pre-specified stopping boundary for non-inferiority was crossed (Median follow-up was 6.9 years). This demonstrates why it is can be difficult to say when an analysis publication should happen.

The trial team found that the amount of time that men lived was not reduced when they had intermittent therapy. And that for many of the men side effects were reduced and could lead to an improved quality of life. The men were followed for an average of around seven years.

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9 A trial looking at intermittent versus continuous hormone therapy for prostate cancer that has continued to grow but has not spread (Intercontinental), CancerHelp UK website, http://www.cancerresearchuk.org/cancer-help/trials/a-trial-looking-at-intermittent-versus-continuous-hormone-therapy-for-prostate-cancer-that-has-continued-to-grow-but-has-not-spread