

Clinical trials : Medical Research Council response to the Committee's third report of session 2013-14 : seventh special report of session 2013-14 / Science and Technology Committee.

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House of Commons
Science and Technology
Committee

**Clinical trials:
Medical Research
Council Response to
the Committee's
Third Report of
Session 2013–14**

**Seventh Special Report of
Session 2013–14**

*Ordered by the House of Commons
to be printed 27 November 2013*

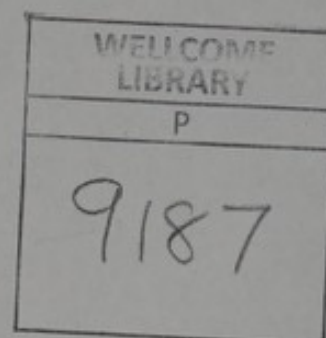
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Seventh Special Report

On 17 September 2013 the Science and Technology Committee published its Third Report of Session 2013-14, *Clinical trials* [HC 104]. On 19 November 2013 the Committee received a memorandum from the Medical Research Council which contained a response to the Report. The memorandum is published as Appendix 1 to the Report.

Appendix 1: Medical Research Council response

The MRC welcomes the Report from the Committee and the careful attention it has paid to critical issues in improving the UK and European environment for clinical trials, as well as increasing public awareness and opportunities for participation in such research. The MRC is grateful to have had the opportunity to provide written and oral evidence, the content of which will not be reiterated in this response. Overall, we support the conclusions and recommendations of the Report and look forward to working with government, regulators, and researchers from academia and industry to help address those that relate to the clinical trial funding, sponsorship and public engagement roles of the MRC.

We note that many of the recommendations are not specific to the MRC and will focus in particular on those that are relevant to our role.

Responses to specific recommendations

11. Clarity in use of the term “clinical trial” is essential. The establishment of consistent terminology would be an important first step towards making the UK an easier place to conduct clinical research. *We recommend that the Government agrees a set of simple definitions for the terms “clinical trial”, “clinical study” and “clinical research” and ensures their consistent use across the Health Research Authority, Medicines and Healthcare Products Regulatory Agency, Medical Research Council, National Institute of Health Research and the NHS.*

The MRC strongly supports this recommendation. As referenced in the report, the MRC uses a definition that is wider than Clinical Trials of Investigational Medicinal Products (CTIMPs) and which is based on the WHO definition of clinical trials. We consider that clinical trials of other interventions, eg surgical techniques; devices or cognitive therapy, should also be registered and reported following the guidance proposed by the Committee.

24. *We urge the Government and MHRA to continue engaging at a European level to resolve these issues and to work together to ensure that, when the resulting legislation is introduced, the administration of clinical trials in the UK will be pragmatic and proportionate.*

The MRC has worked closely with researchers, other funders and organisations to provide a coordinated response to the draft EU Regulation and proposed amendments. We agree

with the Committee that the current direction is overall an improvement, but it is important that next stages of discussions maintain the expected benefits. It will also be critical to ensure that the implementation of the final Regulations puts into operational form a truly risk-proportionate and harmonised approach to approval and reporting of clinical trials.

51. We consider it important that the information contained on the Clinical Trials Gateway is accessible to the lay person, which does not appear to be consistently the case at present. *The Government should ensure that all trials listed on the Gateway include a plain language summary written specifically for a lay audience. Where such summaries are not already in existence, the Government must be prepared to commit the time and effort needed to create them. Taking into account the Gateway's current resource levels, we recommend that, where possible, preparation of a lay summary should be included as a requirement for publicly-funded trials, but that the Government remain open to the option of increasing the level of resource dedicated to the Gateway if necessary.*

The MRC recognises the enormous contributions to medical research made by participants in clinical trials and the need for information to be easily accessible to patients and potential participants. At present, the MRC requires lay summaries on all research funding applications, these will shortly be available for all funded research in the Gateway to Research¹. The MRC also requires all funded clinical trials to be registered. However, we recognise that there is more to be done in making plain language summaries available for clinical trials in any register or trial material and websites. In oral and written evidence to the Committee the MRC highlighted its positive view on Cancer Research UK trials information, but we also recognise the considerable resource challenge to make information on trials across all disease areas available in this way. We will continue to work with other public funders of research on ways to ensure appropriate level information is readily available to the public on trials.

58. Clinical trial transparency is important and greater transparency would be likely to provide a number of benefits, particularly if applied retrospectively. However, there are obstacles to achieving this and the drive for greater transparency must be balanced against other concerns, particularly the need to protect patient privacy. Greater disclosure does not necessarily equate to greater transparency if the information shared cannot easily be understood and *we therefore recommend that efforts to increase the availability of clinical trial data focus on providing information that is accessible, assessable, intelligible and usable.*

The Committee has set out clearly the levels of transparency that should be considered, which reflect MRC policy in this area, and the MRC supports the recommendation that transparency should aim to achieve these aspirations while protecting participant privacy and respecting consent.

63. We consider universal trial registration to be a crucial step in increasing clinical trial transparency and believe that all future trials should be included in a publicly accessible register. This is clearly not the case at present, even for trials conducted in the

¹ <http://gtr.rcuk.ac.uk/>

UK. We recommend that the Government take steps to ensure that, in future, all clinical trials conducted in the UK, and all trials related to treatments used by the NHS, are registered in a WHO-listed primary registry.

The MRC requires that funded clinical trials are registered. We are aware, however, for the need for clarity and consistency of definition of clinical trial in this regard, as outlined under recommendation (11), in order for effective implementation. In addition, it should be noted that clinicaltrials.gov is not included as a WHO primary or partner registry.

64. Since the trials of treatments currently in use often occurred many years ago, retrospective disclosure is important if the benefits of clinical trial transparency are to be realised in the short to medium-term. Although retrospective trial registration will incur some cost, we consider that this will be outweighed by the public health benefit of having a complete picture of the trials conducted on treatments currently available to patients. The Government should support the retrospective registration of all trials conducted on treatments currently available through the NHS and should actively pursue policies to bring this about.

It is desirable that all trials providing evidence relating to current NHS treatments should be registered. However, we would have some concern as to how far retrospective registration could go back—there will be challenges in identifying the research base underpinning long-established treatments and tracing the original trials and sponsors of that work. This may be particularly challenging where established treatments are not medicinal products subject to regulatory submissions. The MRC will endeavour to support the Government in addressing this recommendation as far as is feasible.

68. We consider that summary-level results should be made publicly available for all clinical trials and we welcome the many new media through which it is now possible to share this information. Nevertheless, peer review is vital to the reputation and reliability of scientific research and we deem it appropriate that journal articles remain the primary instrument for the publication of summary-level trial results.

69. Many historic trials remain unpublished, which is far from ideal. However, retrospective publication of all trials of all treatments currently in use, while desirable, would almost certainly be unachievable given the likely time and resources that this would require. We therefore emphasise again the importance of retrospective trial registration as a means of providing a vital “index” against which individual cases of non-publication can be identified and, where of particular importance, pursued on an ad hoc basis.

70. Given recent changes to academic publication models, we do not recognise as legitimate the argument that it is not possible to publish “negative” results in a peer-reviewed journal and we consider failure to publish on a timely basis to be poor scientific practice. However, we are sympathetic to the pressure that scientists are often working under and therefore we urge the Government and other trial funders to ensure that researchers are provided with the time and resources needed to meet their publication obligations.

The MRC expects to provide funding for time to fully analyse and publish all clinical trial outcomes. It is a stipulation of MRC funding (including of clinical trials through both

Developmental Clinical Studies and Global Health schemes) that outcomes must be published. We recognise the need for appropriate support and funding for this stage of the research.

79. It would be unduly burdensome to mandate that clinical study reports (CSRs) be produced for non-commercial trials. We also consider that issues concerning the reliability of the information contained in academic journal articles should be dealt with at source, for example by strengthening the peer review process as recommended in our 2011 Report, rather than by effectively bypassing academic publication through greater reliance on CSRs. We therefore do not support any move to make it mandatory for non-commercial trials to produce a CSR, or any other document of an equivalent level of detail. However, we recognise that CSRs can provide a useful contribution to the scientific literature and, once a regulatory decision has been reached, we see no compelling reason why CSRs should not be placed in the public domain, with identifiable patient data redacted.

The MRC supports this recommendation which reflects our policy on availability of CSRs.

88. We are not in favour of placing anonymised individual patient-level data (IPD) in the public domain in an unrestricted manner, as we consider that the risk to patient confidentiality is too great and, for many past and current trials, this level of disclosure would go beyond the confines of previously obtained patient consent. Nevertheless, we recognise the scientific value of IPD and consider these data to be currently underutilised.

We agree with the Caldicott 2 Review that providing specific individuals with controlled access to personal confidential data such as IPD through carefully managed and secure "safe havens", together with contractual agreements about how that data can be used, is the best way forward. We also consider that access should be facilitated by an independent "gatekeeper", responsible for evaluating research proposals and ensuring that data is handled responsibly and in a way that makes a useful contribution to scientific knowledge.

89. The UK could take the lead in shaping how a global system for sharing IPD for non-commercial trials might operate and a national system covering all non-commercial UK trials would be capable of delivering potentially significant benefits. We consider that the Health Research Authority (HRA) could act as developer, administrator and gatekeeper for a central repository of IPD for non-commercial UK trials. In order to achieve this, *template consent forms provided by the HRA should allow for and emphasise to trial participants the benefits of data sharing. Research Ethics Committees should also take into account any transparency restrictions imposed by patient consent forms when evaluating research proposals for clinical trials.*

These principles on access to individual level data also reflect the position of the MRC. We consider that there may be a range of options for 'safe havens'—some of which already exist. It is our position that data may also be shared through research collaborations. We are working with partners, including the Wellcome Trust and Academy of Medical Sciences (AMS) to clarify the principles and operation of current approaches and how 'safe havens' should optimally be resourced and operated to ensure respect for privacy and

consent, while facilitating the considerable opportunities of increased data access. We will cooperate fully with the work of the NHS and Departments of Health in clarifying optimal approaches for linkage to NHS data.

94. We support the development of the EU Clinical Trials Register (EU CTR) and hope it will also include summary-level results, as promised, by the end of 2013. However, we do not consider the register to represent a complete solution to the problem of nonregistration of clinical trials, as it does not include all the trials that have been conducted on all medicines currently available in Europe. *The Government should encourage the EMA to further increase the scope of the EU CTR, for example by including phase I trials and trials conducted outside of the EU. We also recommend that the Government monitor the EMA's fulfilment of its pledge to include trial results on the register and obtain an explanation if the EMA fails to do so by the end of 2013.*

We understand that phase I trials of IMPs will be included in the scope of the revised Directive which includes assessment of adverse effects of relevant products.

99. As a major direct and indirect funder of clinical trials, the Government can influence behaviour across both the public and charitable sectors. This influence has not been wielded effectively to increase transparency, meaning that many publicly funded trials remain unregistered and unpublished. *We recommend that registration in a WHO-listed registry and publication of summary-level results in a peer-reviewed journal be made contractual requirements for all publicly-funded trials, including research supported by the Charity Research Support Fund. The wording of these requirements should be standardised across all contracts to ensure consistency. We also recommend that public funders of research rapidly put in place mechanisms to monitor compliance with transparency policies and ask the Government to detail in its response to this Report how and when this will be done.*

It is a requirement of MRC-funded trials that they are registered and summary results published. Where this has not occurred within a specific time frame, our initial audit suggested that it is usually due to differences in definitions of clinical trials (addressed above) or the need for additional time for follow-up and analysis. We are reviewing how the ResearchFish system for collating research outcomes could be expanded to provide a valuable interface between funding portfolio, trial registration and published outcomes thereby allowing effective monitoring of registration and publication requirements without duplicative or disproportionately burdensome reporting requirements.

100. Since the Government has encouraged industry to disclose retrospectively the results of past trials, we think that it should be prepared to do the same for the major trials that it has funded. *We therefore recommend a retrospective audit of all public phase III trial grants awarded since 2000, followed by action to ensure that any failures to register or publish the summary-level results of these trials are rectified within 12 months.*

Any failures to correct these mistakes should be taken into account when considering future grant applications from principal investigators of previously unregistered or unpublished trials. In future, for grants awarded to fund phase III clinical trials we suggest that the MRC and the NIHR allocate a small proportion of funding to cover the

time and resource requirements of preparing a manuscript for publication, and withhold this funding until the results of the trial are ready to be published.

We agree to this recommendation to extend the previous audit from 2006 to 2000, including confirming previous initial findings. We recognise the need to agree a consistent definition of studies that will be in scope of this review as phase III trials. Through the ResearchFish system, the MRC will ask for confirmation of trial registration within a year of funding. At present, the MRC's portfolio of phase III trials is almost exclusively in global health, non-UK (and non-EU) based studies. Imposing funding limitations in these, often very resource-poor, environments may not be practical as the research institutions involved may not have the capacity to backfill delayed awaited funding, thus this requirement could disincentivise rather than facilitate publication. We will review and ensure that the requirement to publish results is clear and we will monitor this and follow-up any funded trials that are not published in a reasonable time scale.

101 ...We suggest that the academic publishing industry put in place robust measures to ensure that unregistered trials are not just rejected, but that the trial sponsor(s) and funder(s) are notified that the trial has not been properly registered.

We would welcome this additional check on compliance with registration requirements.

110. Research Ethics Committees should have a role in considering and monitoring compliance with transparency policies. As such, we welcome the HRA's new transparency policy and support, in principle, the proposals made in its May 2013 paper. We recommend that the HRA initially retains full responsibility for policing its own policies and ensures that all trials have been registered and published according to an agreed timeline, rather than performing checks on a sample basis. In addition, there must be penalties for non-compliance. We recommend that the HRA provides us with a progress update on implementation of its new transparency policy by the end of 2013.

We recognise the importance of HRA responsibility in this; we are in discussions with HRA and other funders to determine whether a consistent system can be used for registration and monitoring to ensure that researchers are not unnecessarily burdened with duplicative reporting requirements. This has led to consideration of the potential for linkage of trial registries with ResearchFish and PubMed resources and back to ethics approval data.

122. Increased transparency is unlikely to lead to improved medical outcomes unless mechanisms are in place to ensure that emerging evidence is quickly and effectively incorporated into clinical practice. Given the high degree of reliance placed on NICE's guidance by health professionals, we consider it essential that this advice remains fully up to date and that processes are in place to ensure that emerging evidence is rapidly incorporated. The Government should ensure that, as improved transparency leads to ever greater volumes of trial data becoming available, NICE continues to receive the resources it needs to assimilate emerging evidence into its guidance in a timely manner.

This is a very important area and one that the Committee has rightly emphasised. Through our methodology research programme, the MRC is working with policy partners, including NICE, to ensure that innovative methods are available to deal with rapidly expanding availability of data—both from increased clinical trial transparency but also

other approaches to research, such as medical bioinformatics and population-based research.

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