

# MRC Clinical Trials Transparency Review

## Final Report (November 2017)

### Background

1. In 2010, a systematic review demonstrated that around half of all clinical trial results have never been published.<sup>1</sup> Therefore there is a risk that valuable research findings are not available to the scientific and clinical community, and that this could lead to ineffective or harmful drugs being marketed.
2. All researchers are encouraged to prospectively register their clinical trials, to make their study design and methods public, and to make their study findings publicly available. Since 2005, many journals will only publish results from prospectively registered clinical trials and, since 2013, AllTrials have campaigned actively for the registration and publication of all clinical trials.

### The MRC Evaluation of Policy and Practice (2013)

3. In 2013, the MRC evaluated its portfolio of clinical trials supported between 2009 and 2012. This demonstrated that the MRC:
  - supported over 120 live clinical trials through the Developmental Clinical Studies scheme, intramural funding for clinical trials units, and through the Joint Global Trials programmes,
  - provided approximately £20million each year for clinical trials funding.
4. The evaluation found that:
  - 94% of MRC-funded trials commenced before 2012 were registered,
  - 89% of trials completed by February 2012 had published findings; 72% within one year.

### Actions

5. Since 2013, the MRC has required the public registration of MRC-funded clinical trials and promoted the publication of findings within 12 months of trial completion through the award letters for schemes that fund clinical trials:
  - Registration of clinical trials was included in the MRC Additional Terms and Conditions in December 2015 and updated in 2016 to specify registration in the ISRCTN registry,
  - The MRC requirements for trial registration, publication and data-sharing we outlined in the MRC Policy on *Open Research Data: clinical trials and public health interventions*<sup>2</sup>(published October 2016 and updated in August 2017<sup>3</sup>),
  - The MRC joined the AllTrials Campaign in 2013 and was a co-signatory to the *WHO Joint Statement on the Public Disclosure of Results from Clinical Trials*<sup>4</sup> in 2017.

### MRC Clinical Trials Transparency Review (2017)

6. This review updated the earlier evaluation of the MRC clinical trials portfolio and included additional data on registration and publication collected via researchfish® between 2013 and February 2016. The review included trials supported by directly-funded MRC awards made during the five-year period from February 2011 to February 2016. Excluded from the review was funding provided for trials through the Efficacy and Mechanism Evaluation (EME) programme (a partnership with the NIHR to which the MRC contributes £11 million per year), intramural funding for clinical trials units and

<sup>1</sup> Song F, Parekh S, Hooper L, et al. Dissemination and publication of research findings: an updated review of related biases. *Health Technology Assessment* 2010;14:8:1-93.

<sup>2</sup> <https://www.mrc.ac.uk/research/policies-and-guidance-for-researchers/open-research-data-clinical-trials-and-public-health-interventions/>

<sup>3</sup> <https://www.mrc.ac.uk/documents/pdf/mrc-policy-on-open-research-data/>

<sup>4</sup> <http://www.who.int/ictpr/results/jointstatement/en/>

centres, as well as funding for the Methodology Research Programme (around £4m per year) and Methodology Hubs for Clinical Trials.

7. To define the awards to be included in the 2013 and 2017 reviews, the broad WHO definition of clinical trial was applied: “any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes”.<sup>5</sup> Specific objectives for the review were:

- to estimate the number of ‘live’ clinical trials funded by the MRC during the period and the value funding awarded,
- to estimate the proportion of clinical trials that are publicly registered, and evaluate the registration,
- to estimate the proportion of completed trials that have published within one year of completion or subsequently, and the proportion that fail to publish,
- to review information on data-sharing, published datasets, curation/managed access to clinical trials data by external users.

8. The review used information on the outputs, outcomes and impacts that have arisen from MRC-funded research which is submitted annually by award holders, funding award details and any publications linked to trial registry numbers. If a trial registration number had not been submitted a manual search of clinical trials registries and Google was undertaken; researchers of 25 studies were contacted directly.

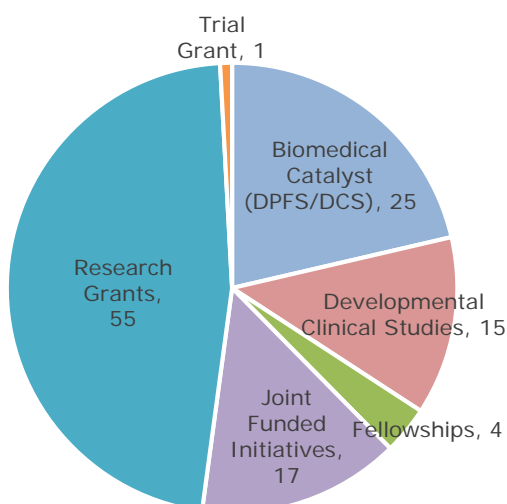
## Review Results

### Funding awarded (2011-2016)

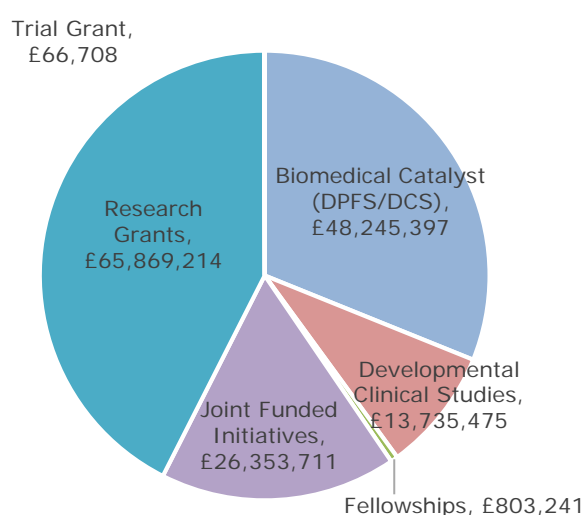
9. From 01/02/2011 to 01/02/2016, the MRC made 117 awards that included a clinical trial, committing a total of £155 million (£30m per annum; *Figure 1*). Awards included Developmental Clinical Studies (e.g. Biomedical Catalyst and Developmental Pathway Funding Schemes), Fellowships, joint-funded partnership initiatives (e.g. Global Health/DFID programme) and Research Grants.

*Figure 1: Number and value of awards by funding scheme, 2011-2016*

**Number of awards, 2011-2016**



**Award value (£) 2011-2016**

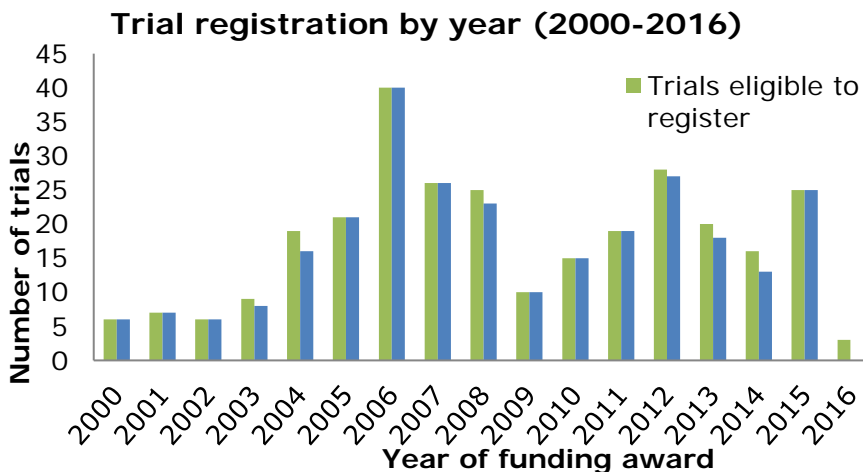


<sup>5</sup> [http://www.who.int/topics/clinical\\_trials/en/](http://www.who.int/topics/clinical_trials/en/)

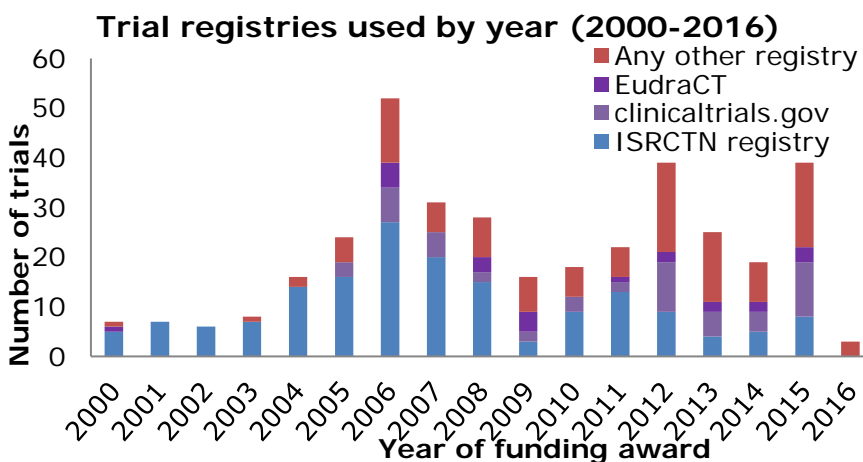
*Trial registration*

10. Of the 117 awards, 107 had started and were required to register, 10 awards had not yet started. Of the awards that had started, 101 (101/107, 94%) trials were registered. Six trials started without registering, including five trials of a non-regulated intervention (i.e. not involving investigational medical products [IMPs] and therefore regulated under the EU Clinical Trials Directive). There was no increase in the proportion registering since the 2013 review (94%).
11. Trial registration numbers had been provided by researchers for 37% (40/101) of the registered trials. The remaining registration numbers were identified through manual searching or direct enquiry with researchers.
12. Thirty-seven of the registered trials (37/101, 36.6%) were registered with the ISRCTN<sup>6</sup> (International Standard Randomised Controlled Trials Number) registry. This is a World Health Organization (WHO) primary registry and the registry named in MRC terms and conditions since 2013. MRC will fund the costs of registration with the ISRCTN registry. The remaining trials were registered with clinicaltrials.gov<sup>7</sup> (a US-based registry that does not meet the WHO primary registry criteria) and EudraCT (a registry of trials conducted under the EU Clinical Trials Directive).
13. In *Figure 2*, the number of MRC-funded clinical trials registered are shown by year since 2000 and, in *Figure 3* the number registered in the ISRCTN or other registries are shown.

*Figure 2*



*Figure 3*



<sup>6</sup> <https://www.isrctn.com/>

<sup>7</sup> <https://clinicaltrials.gov/>

### *Trial publication*

14. Forty of the 101 trials had been completed for 12 months or more by June 2016. Thirty-three (33/40, 82%) had reported at least one publication and 26 (26/40, 65%) had reported at least one publication within 12 months of the award end date (i.e. during the final year of the award or up to 12 months after) so were more likely to report main trial results. Importantly, three of the seven trials with no publications had ended more than 24 months previously.
15. Of 33 trials with reported publications, the main trial results were clearly identified in the publication for 14 (14/33, 42.0%) trials, although two of these publications were more than 12 months after funding award completion and one was published within the timeframe of an extension to the original award. For the remaining 19 trials with publications, 15 published within 12 months of award completion and four published later; we could not identify a publication reporting the main results among these.

### *Sharing data*

16. There were 24 (24/107, 22%) trials which started during the review period that had created a database or collection for sharing. Seven of these datasets (7/24, 29%) had already been shared with other researchers.

### **Summary of findings**

17. The MRC funds around 120 clinical trials each year and spends around £30m per annum on clinical trials.
18. There were 107 MRC-funded clinical trials which started during the five years from 2011 to 2016, of which 94% were registered in a clinical trials registry. The proportion of trials that are registered remains the same as in the previous evaluation in 2013. Notably researchers failed to register six trials before these started and only one-third of registered trials were in the ISRCTN registry, that specified in MRC policies and terms and conditions.
19. By the end of the five-year review period, 40 trials had been completed for at least one year, however based on information submitted to MRC only 82% had at least one publication and three trials had been completed for over two years without publishing results. Around 65% of studies reported a publication within 12 months of the award end date, but under half of these were the main trial results. Over one-fifth (22%) of registered trials had reported a dataset as an output, and seven of these had reported sharing with other researchers.
20. Although MRC-funded trial registration is over 90%, the review has identified a lack of awareness among some researchers of the need to register all trials that meet the WHO definition, including those that do not involve investigational medical products, and so are not defined as clinical trials under the EU Clinical Trials Directive, and clinical studies that are early phase or use non-traditional study designs (e.g. proof-of-concept trials, three-way crossover studies). Moreover, two-thirds of trials were not registered in the ISRCTN registry despite this being an MRC requirement and funding being available to cover the registration cost.
21. Since October 2016, the MRC policy on registration has applied to public health interventions as well as clinical trials. To raise awareness, these changes to the policy are publicised on the MRC website, and registration and publication requirements are included in the terms and conditions and award letters for all relevant funding schemes.
22. There were limitations to tracking registration through the annual output, outcome and impact returns as researchers can only enter the clinical trial registration number retrospectively, and there is a similar delay in reporting publications.
23. A number of recommendations have been identified resulting from the review. The MRC is currently taking these forward.

## **Recommendations from the 2017 Review**

### ***Raising awareness***

- Applicant guidance should be revised to
  - highlight the requirements around the registration of clinical trials, clinical and public health intervention studies,
  - clarify the funding available to support registration fees, and
  - provide a link to the *MRC Policy on Open Research Data: clinical trials and public health interventions (2016)*.
- Researchers and MRC's research programme staff should be made aware of the broader scope of the *MRC Policy on Open Research Data: clinical trials and public health interventions*. and, specifically, the requirement to register all clinical and public health intervention studies involving human participants;
  - Specific communications should be targeted at researchers undertaking clinical, behavioural or public health intervention studies,
  - Internal awareness-raising should be undertaken with MRC staff involved in managing relevant research schemes,
  - Data-sharing and publications, as well as registration should be emphasised.
- Results of the MRC 2017 review should be made available on the MRC website and communicated to external users via social media as appropriate.

### ***Post-award monitoring***

- The annual invitation to researchers to provide information on outputs, outcomes and impacts should specifically highlight the requirement to provide registration and publication details for clinical trials and intervention studies,
- The process for identifying studies meeting the clinical trials definition could be improved, for example by prospectively flagging these studies at the time of the funding award,
- The collection system should be reviewed to explore how registration data can easily be entered for all relevant studies, including for clinical and public health intervention studies.

### ***Additional tracking and monitoring***

- The MRC should explore methods for automating tracking of study registration and publication, and defining the clinical studies portfolio in order to improve annual monitoring,
- The MRC should work with the ISRCTN registry and WHO Clinical Trials Registry Platform to explore ways of accessing and extracting registration data on MRC-funded studies to improve monitoring
- The MRC should collaborate with the ISRCTN registry, WHO Clinical Trials Registry Platform and AllTrials campaign to explore the potential for improving the recording and identification of main results publications in trial registries to improve monitoring of outputs.

### ***Future review***

- The MRC review should be repeated (after an appropriate interval) to evaluate improvements resulting from new policies and awareness-raising, with an additional focus on data-sharing,
- The review results should be used to validate any changes to automated monitoring and evaluation systems.