

Update of the 2013 review of MRC clinical trials awards between 2009 and 2012

Background

A review was undertaken by the MRC in 2013 to define the portfolio of clinical trials supported by MRC funding that were 'live' (ongoing) between 2009 and 2012, determine whether trials were publicly registered and document publication rates. The results of this review were reported publicly.[ref to the House of Commons Science and Technology Committee and MRC website] The broad WHO definition of clinical trial was used: "*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*".¹ As the responsibility for funding phase III trials in the UK was transferred to the NIHR in 2006, most of the studies funded were early phase trials funded through research grants within the Developmental Clinical Studies scheme. However some late-phase trials were supported through research fellowships and research grants within the Joint Global Health Trials programme. In addition, the MRC continued to support the MRC Clinical Trials Unit at UCL and MRC Population Health Research Unit at the University of Oxford.

Findings from the 2013 review of MRC-funded clinical trials

The review of awards made between 01/02/2009 and 01/02/2012 that included a clinical trial demonstrated that the MRC:

- supported over 120 live clinical trials through the Developmental Clinical Studies scheme, the MRC Clinical Trials Unit at UCL and MRC Population Health Research Unit at the University of Oxford and through the Global Trials programmes
- provided approximately £20m pa for clinical trials funding, excluding intramural (institute/unit/centre) support
- was funding trials in partnerships such as the National Prevention Research Initiative (NPRI) and the Global Health/DFID programme
- was funding a programme of Methodology Research at £4.5m and had committed £8m to Hubs for Trials Methodology Research
- funded the Efficacy and Mechanisms (EME) Programme (£13m) administered by NIHR.

At the time of the review, using data entered into the database before 01/02/2013, the key findings in relation were that:

- 94% of clinical trials funded before 2012 were registered
- 89% of clinical trials completed by 01/02/2012 had published; 72% within one year.

Scope of the review update in 2017

As part of the 2017 MRC review of clinical trials, information was obtained from the annual outcomes, outputs and impact monitoring returns (submitted via Researchfish®) for funded awards that were 'live' between 01/02/2009 and 01/02/2012 in order to confirm and update the initial

¹ http://www.who.int/topics/clinical_trials/en/

findings from the 2013 review. Data entered into the database up to 01/02/2016 were available for review.

The aims of the update were to determine whether:

- the proportion of studies registered in a publicly registry (including retrospective registration) had increased, and
- the proportion of studies that had published findings had continued to rise since 2013 as late-reporting studies published their results.

Awards made prior to 01/01/2007 were excluded from the update as these included late-phase trials that had subsequently transferred to the NIHR in 2007. Trials supported by MRC between 2000 and 2006 are reviewed elsewhere.

Clinical trials were not identified consistently by a 'flag' in MRC systems, therefore keyword searches were used to identify clinical trials and a manual review undertaken to confirm the selection. Clinical trials directories were not maintained after the electronic research database was established in 2006, therefore these were not searched. Studies included in the review were clinical trials of investigational medicinal products (IMPs), licensed medications, devices and behavioural interventions.

Although the review update was designed to be as close as possible to the original review in 2013, the original dataset was not available to us as the relevant systems had been revised and improved since this time. It was not possible to replicate the earlier review exactly nor to determine whether the same studies had been included or excluded and this has led to some discrepancy in findings.

The review update included:

- existing awards that commenced on or after 01/01/2007 and were continuing after 01/01/2009
- new awards commencing between 01/01/2009 and 31/12/2012.

Joint global health trials were included in the review, as were trials that were funded by research grants or fellowships to applicants based within MRC Centres and Units, such as the Clinical Trials Unit. However, trials funded by intramural funding or NIHR EME Programme funding were not included. All phases of clinical trial were included.

Findings from the 2017 review update of 'live' trials awards between 2009 and 2012

There were 95 clinical trials identified as 'live' during the review period, of which 93 (98%) were registered, either prospectively or retrospectively, in a public registry and 59 (71% of 93) were registered in the ISRCTN registry. There were two trials that were never registered; neither of these involved an IMP.

Of the 95 trials identified,

- 9 awards had not ended by 01/02/2016, however 7 of these had already published interim findings or protocols.
- 86 funding awards had ended by 01/02/2016.

Of the 86 completed awards²,

- 84 (98%) were associated with at least one publication:
 - 61 (71% of 86) had published by one year of the award end-date;
 - 15 (17% of 86) had published between 12 and 24 months after the award end-date;
 - Eight (9% of 86) had published findings more than 24 months after the award end-date; the median time to publication after award end was 33 months (interquartile range 28, 35 months) and all had published by 48 months;
 - Two (2% of 86) studies had published no findings (awards had ended 16 and 75 months prior to 01/02/2016).

Principal investigators for the two unpublished studies were contacted. Findings from the older trial (completed for 75 months) had been recently submitted for publication.

Summary

For 'live' clinical trials funded by MRC between 2009 and 2012:

- the proportion registered in a public trials registry increased from 94% (in 2013) to 98% (in 2017);
- 98% of clinical trials had published results; 88% published within two years and 71% published within one year;
- Of the two unpublished trials, one had been recently submitted for publication.

² Only 36 of the 86 awards had been completed by 01/02/2012, and were likely to have been included in the original dataset reviewed in 2013. Of these, 35 were associated with at least one publication:

- 30 (84% of 36) had published within two years; 24 (67%) within one year;
- 5 (14% of 36) had published more than two years after the award end-date (median time to publication 32 months; interquartile range 28, 35 months);
- 1 (1% of 36) study had published no findings.

Although as far as possible the same parameters were used to define this dataset as for the 2013 review, we did not have access to the original dataset hence the findings on publication are slightly discrepant.

Review of MRC Phase III clinical trials awards between 2000 and 2006

Summary

There were 124 awards for Phase III clinical trials made by the MRC between 2000 and 2006 but two of these trials were discontinued.

Of 122 trials³ completed,

- 97% were publicly registered in a trials registry;
- 81% of trials published within two years of the award end-date (63% published within 1 year);
- 19% of trials published more than two years (median 35 months) after the award end-date, however one-third of these trials had published interim results or a protocol before award end.

Background

Awards made by the MRC within the period 2000 to 2006 included all phases of clinical trials, including Phase III trials. After 2007, responsibility for funding Phase III clinical trials in the UK was transferred to the NIHR Efficacy and Mechanism Evaluation (EME) Programme, which is co-funded by the MRC. Since the portfolio transfer, the MRC has predominantly funded early phase (Phase I and Phase II) trials in the UK, and funding for Phase III trials has been limited to global health (non-UK and non-EU) trials, or public health and behavioural interventions.

The MRC requires researchers to publish the main findings from a clinical trial within 24 months of the award end date, however researchers are strongly encouraged to submit main trial findings for publication within 12 months of the end-date.

Review of clinical trials funded by the MRC between 2000 and 2006

In 2017 review of clinical trials, we identified all 94 awards for Phase III clinical trials funding between 01/01/2000 and 31/12/2006 using keyword searches and a manual review to confirm the selection. We also searched the archived clinical trials directory and identified 30 additional trials commencing before 2006. The phase of each trial was determined by manual check of the award summary, trial registry entry and/or publications.

Although researchers entered publications into the registry, these were incomplete and did not identify publication of the main findings. Additional publications were identified by automated searches of EuropePMC, manual searches of registry entries and the PubMed database. A manual check was undertaken to identify the date of the publication that included the main trial findings and publications within 12 months of the award end-date.

Two of the 124 awards for Phase III trials were excluded from the review as they did not progress⁴. Nine global health trials were included⁵, as were seven trials taking place within the MRC Clinical Trials Unit at UCL.

³ Figures updated (on 29 January 2018) from 77 to 78 trials published within 12 months of completion due following information received from the researcher about publications not reported through Researchfish®.

⁴ One trial was stopped when it failed early feasibility testing, while a second trial with negative interim results was stopped after a similar US trial also reported negative findings.

⁵ These were manually cross-checked with the global health trials portfolio list in 2013 which included all Phase III global trials managed and funded by the MRC at the time of the transfer of the main trials portfolio to NIHR

Trial registration

Of the 122 trials that completed, 120 (97% of 122) were registered in a public trials registry; 103 registered in the ISRCTN registry (a WHO primary registry) and 17 in other registries (nine in clinicaltrials.gov, four in EudraCT and five in UK CRN). Some trials were noted in the registry to have been retrospectively registered.

The four trials that did not register included one involving a licensed medication, one of a carer intervention, one of a psychological intervention and one of a physiotherapy intervention.

Trial publication

During the period of this review, the MRC required publication within a 'reasonable' period but did not specify further the timeframe for publication.

All 122 awards⁶ had ended by 2014 and of these:

- 78 (64% of 122) had published findings from the trial within 12 months of the end date of the award (i.e. within the 12 months prior to, or the 12 months after, the award end date);
- 21 (17% of 122) had published between 12 and 24 months after the award end date;
- 23 (19% of 122) had published the main trial findings more than 24 months after the award end date.

The median time to publication for 23 trials that published more than 24 months after the award end was 35 months (interquartile range 28, 50 months). Eight of these trials led to one main results publication, and 15 trials were associated with a median of three publications each. A paper reporting the protocol or interim results had been published during the award period for eight trials.

⁶ See note 3