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Research and policy impact of trials published by the UK National Institute of Health Research (2006-2015)

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Impact of UK NIHR clinical trials

HIGHLIGHTS

- The instrumental use of a randomised controlled trial in systematic reviews and policy and guidance documents represents an easily quantifiable but important dimension of impact
- This analysis has found that randomised controlled trials funded by the NIHR and published in the HTA journal series and related journals have impressive citation rates and a sizeable proportion are certainly being used in key publications in a genuinely instrumental manner.

Concise summary:

Randomised controlled trials funded and published by the NIHR have impressive citation rates and many are used in research and policy in an instrumental manner.

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ABSTRACT:

OBJECTIVES:

Health Technology Assessment (HTA) aims to inform and support healthcare decision-making and trials are part of that process. The purpose of this study was to measure the impact of a sample of trials in a meaningful but robust fashion.

METHODS: All randomised controlled trials funded and published by the UK National Institute of Health Research (NIHR) in the Health Technology Assessment journals series and other peer-reviewed journals were identified for 2006-2015. Citation analysis was performed for all trials, and quantitative content analysis undertaken on a purposive sample to determine if impact could be categorised as 'instrumental', i.e. having a clear influence on key research and policy publications.

RESULTS:

The search identified 133 relevant trials. Citation rate per trial was 102.97. 129/133 (98%) of trials were cited in one or more systematic reviews or meta-analyses (mean per trial 7.18, range 0-44). Where they were cited, the trials were used in some form of synthesis 63% of the time. 91/133 (68%) of trials were found to be cited in one or more guidance or policy document (mean per trial 2.75, range 0-26), and had an instrumental influence 41% of the time. The publication of these trials' results in journals other than the Health Technology Assessment journal appears to enhance the discoverability of the trial data. Altmetric.com proved to be very useful in identifying unique policy and guidance documents.

CONCLUSION:

These trials have impressive citation rates and a sizeable proportion are certainly being used in key publications in a genuinely instrumental manner.

I. INTRODUCTION

Health Technology Assessment (HTA) aims to inform and support healthcare decision-making[1]. Randomised controlled trials are part of that process. They have an inherent value in that they provide an answer to a question where previously there had been uncertainty (equipoise). However, 'value' is a much-debated and multi-dimensional concept and a randomised controlled trial's value must extend beyond providing an answer to a question. It should have some demonstrable impact too[2]. However, assessing the impact of research presents many problems. First, there are many available models for doing so, but all have limitations[3,4]. Second, there is the definition of the term 'impact' itself. The measurement of impact can range from counting the number of times a piece of research is cited by others, to its generation of social, economic or health benefits beyond academia[3,5]. The former, the simple citation of research, is now recognised as a rather limited metric of either impact or quality[6,7]; it does not indicate how the research was used or its possible level of influence on other research[8]. The latter, the demonstration of benefits beyond academia, is undoubtedly more meaningful, but is also more difficult to determine. Consequently, there is potential value in examining not only those publications that are citing the research, but also how they are using it. In this way, it is possible to generate more meaningful data, while also exploring the broader impact of research.

This study aims to show that a particular approach to analysing citation data can provide greater insight into the impact of a particular body of research. In the payback framework of impact, a link is made between the primary and secondary outputs of research, in other words, between the original journal article and its use by other outputs.[3,9] In the case of randomised controlled trials, relevant secondary outputs include, most obviously, policy and guidance documents, but also systematic reviews and meta-analyses[10], which represent an influential form of evidence in the production of much policy and guidance[11,12,13]. Indeed, current published research on this topic has recognised that, 'there is merit in using existing systematic reviews to assess the impact of trials'[10] and that this knowledge gap remains to be filled. The trials funded by the UK National Institute of Health Research (NIHR) represent an obvious sample on which to conduct this work. This funder has previously sought to gauge the impact of the research it funds, for UK HTA projects generally, based on numbers of publications, basic citation analysis or a small number of individual case studies, testing authors' perceptions of the impact of their research[10,14]. This has included an evaluation of the use and weighting of some HTA trials in meta-analyses in Cochrane's reviews[10], but not their use in non-Cochrane reviews, other types of synthesis, or in policy or guidance documents. The aim of the present research is to extend this previous work by quantifying the impact of randomised controlled trials,

published in the NIHR Health Technology Assessment journal, based on the use of these trials in specific types of citing publication: systematic reviews and meta-analyses, and policy and guidance documents.

II. METHODS

Sample

This study is a citation analysis, with quantitative content analysis, of a sample of randomised controlled trials published in the NIHR Health Technology Assessment (HTA) journal. The HTA monograph is a peer-reviewed, open-access journal. Each issue is dedicated to a single project, such as a randomised controlled trial. To be included in the sample for this analysis, the publication had to be a randomised controlled trial funded by the UK NIHR and published in the HTA journal series from 2006 to 2015. A 10-year period of publications was chosen to enable the creation of a sizeable sample with substantial citation data; this would minimise the chance of findings being heavily skewed by results from a single year or a small group of atypical publications, and also controlled for potential long-term impact[3]. The date limit of 2015 permitted sufficient time for included trials to have generated citations up to the point of this analysis. To identify these trials, a search was conducted in MEDLINE, which fully indexes the HTA journal, for randomised controlled trials on any topic published in the HTA journal series from 2006 to 2015 inclusive. The results were then screened using the inclusion criteria described above and the following publication types were excluded: pilot, exploratory or feasibility trials; and studies evaluating methods of recruitment to trials. The result was a sample of all randomised controlled trials published in this journal series for a 10-year period. HTA journal publications contain the full report of each trial. This might include not only the trial's effectiveness findings, but also an economic evaluation and, in some cases, additional but related work, such as a qualitative study. These separate elements of the project might also be published in other peer-reviewed journals, which have more restrictive word-counts but also have the potential to increase the visibility and discoverability of the research[14]. In order to gain a fuller picture of the impact of this set of HTA journal trials, these related publications (effectiveness / efficacy results only) were also included in our sample. These additional, related publications were identified from a combination of sources: first, the trials' project webpages hosted by NIHR; and second, a search in the Science Citation Index (Web of Science).

Citation analysis

Citation analysis represents a conventional and robust approach to gauging a type of research impact. This approach tends to focus on a single funder; uses a single type of research project (e.g. trials) as the unit of analysis; and applies 'forward tracing' (identifying publications that cite the index publication)'[15]. In this case, the aim was to identify publications or documents that cited each HTA journal trial publication. To do this, a search was conducted in September and October 2018 in the Science Citation Index (Web of Science) to identify publications citing the HTA journal trials in our sample. This database was used because it is a highly comprehensive citation index and facilitates searching and downloading of results. The following citation data were then extracted for each HTA journal trial publication, as well as each related journal publication, and entered into Excel spreadsheets (see Supplementary file 1): total number of citations per trial; number of unique Cochrane and non-Cochrane systematic reviews and meta-analyses citing each trial; number of unique policy, practice or guidance documents or publications citing each trial. The two sets of data for the HTA journal publication and any related publication were then integrated (counting only once any systematic reviews and policy documents that cited both the HTA and its related publication). The 'policy' publications included any document described as guidance, guidelines, recommendations, position or consensus statements, or similar publication from national bodies, e.g. National Institute of Health and Care Excellence (NICE), or named specialist society, college or association (e.g. European Society of Cardiology, American College of Gastroenterology or the British Thoracic Society). This is not to claim equivalence between the potential impact of guidelines produced by national bodies, such as NICE, and specialist societies, but rather the aim was to capture the meaningful uptake of the trial evidence within different types and levels of publications that have the greatest potential to impact actual practice. Given that such policy and guidance documents can be difficult to find and many will not be catalogued in standard databases, a complementary search was conducted for each trial using the policy score facility of Altmetric.com®, which identifies web-based policy and related documents[16]. Altmetrics are alternative indicators of interest relating to scholarly outputs, most notably journal publications. Altmetric.com® are one of the pioneers in the use of altmetrics to provide useful insights into how a piece of research is communicated across the Web, primarily on traditional and social media platforms. In 2014 Altmetric.com® started searching for policy document mentions of research on the web, given such evidence was not indexed in traditional research databases. Altmetric.com® does this by tracking a broad range of policy sources directly from organisational websites. This is not an exhaustive list of policy documents but is updated when new policy sources are identified by Altemtric.com® or their users[17]. The policy documents within those websites are then searched for citations of research papers via

unique IDs, link searching and text mining. The complete citation data collected were tabulated and descriptive statistics were produced.

Quantitative content analysis

The citation analysis provided data on how often each trial had been cited overall, and how often by relevant 'secondary outputs', i.e. systematic reviews/meta-analyses, and policy or guidance documents. However, this is a limited metric; as noted above, it does not indicate how the research was used or its possible level of influence on other publications[8]. Greater scrutiny of the citation was therefore required. To do this, quantitative content analysis[18] was conducted on a subset of the total sample in order to determine how these trial publications were actually being used in these two subsets of relevant secondary outputs[8,19]. All included trials were sampled purposively to select those with extensive, relevant citation data across both types of secondary outputs. This sample was therefore composed of all HTA journal trial publications cited in at least one systematic review *and* at least one policy document, supplemented by related publications in other journals satisfying the same criteria but where the trial was not already identified from the HTA journal publication set. The aim was to compile an extensive and useful set of data for in-depth analysis, representing at least 50% of the whole 10-year sample, in order to test how these trials were actually used within relevant publication types.

In the quantitative content analysis, the impact of each published trial on the citing systematic review, policy or guidance document was categorised as either 'instrumental' or 'symbolic'. This terminology is commonly used in the research and policy impact literature[3,15]. Instrumental use refers to 'the explicit application of research to address a policy problem; where research influences issue identification, policy refinement, definition or implementation in a direct and potentially measurable way … that is, policymakers are aware that they are using research in this way and there may be evidence supporting claimed instances of use'[14]. Symbolic use of a piece of research is when it has been used 'to justify a position or specific action already taken for other reasons or to obtain specific goals based on a predetermined position'[14]. In previous studies, the vast majority of citations analysed have been found to be 'symbolic', that is, a 'reference in passing', providing only the most general support for a chosen approach, rather than representing anything more meaningful[3,19]. In this study, to be categorised as 'instrumental' impact in policy or guidance documents, the trial had to have clear supportive link to a recommendation or statement: it had to be one of only a small number of studies (1, 2, 3 or 4) supporting a recommendation. If this level of influence was not apparent, or the trial reported a finding different from the

recommendation, then the trial's citation was categorised as 'symbolic' for that piece of guidance. Applying the same principles to citing systematic reviews/meta-analyses, the trial had to be used in the actual synthesis to be categorised as having an 'instrumental' impact, otherwise its impact was categorised as 'symbolic' only.

III. RESULTS

The total number of NIHR-funded randomised controlled trials published in the HTA journal series for the 10 years between 2006 and 2015 was n=133. These were all clinical effectiveness or diagnostic accuracy randomised controlled trials, 40 of which were described as pragmatic randomised controlled trials. 119 trials also included a cost-effectiveness analysis or other economic evaluation. Additional elements reported in the HTA journal publications related to the trials in this sample were qualitative (n=20) and observational studies (n=9). Two trials experienced recruitment problems[20,21], although both had citation data. Related publications reported the effectiveness results of 82 of these 133 trials in journals other than the HTA journal series. A typical example is provided by the COMICE trial, the effectiveness results of which were published in both the HTA journal[22,23]and The Lancet[19]. There has been a marked increase in the numbers of trials published over this period, although with the odd exception the proportion of trials with both an HTA and related but separate publication has remained fairly stable (Figure 1).

Figure 1: Numbers of HTA journal trials and numbers with key related publications by year of publication in the HTA journal

Citation analysis

The citation data are presented in Table 1 (the complete data sheet is available as Supplementary file 1). The basic mean citation rate per trial was approximately 103. Across both the HTA and related publications, 131/133 (98%) of the trials were cited in either a systematic review or meta-analysis, or in a policy or guidance document; only two trials (2%) were not found in this analysis to be cited in any potentially relevant document[24-25]. 129/133 (97%) trials were found to be cited in one or more systematic reviews or meta-analyses, the vast majority of which were non-Cochrane reviews (84%). 91/133 (68%) of trials were found to be cited in one or more documents of guidance

or policy. The number of citing systematic reviews and meta-analyses per trial ranged from 0 to 44, and policy and guidance documents per trial from 0 to 26.

<Table 1>

The publication of trials' effectiveness findings in journals other than the HTA journal has a clear influence on the citation metrics. These related publications achieve twice the mean number of citing reviews and more than four times the mean number of citing policy/guidance documents than the HTA journal publication: 125 vs 25 citations per trial; 7.16 vs 3.32 reviews per trial; 3.59 vs 0.80 policy/guidance documents per trial (Table 1). This is important because the original 82 HTA journal publications for these 82 related publications reflected the mean rates for the 133 HTA journal publication sample as a whole: means of 25.95 vs 25.36 citations, 3.55 vs 3.32 reviews, 0.80 vs 0.80 policy/guidance documents. Sixty-six systematic reviews/meta-analyses and 29 policy/guidance documents cited both the HTA journal publication and the related publication. When the data from both the HTA journal and their related publications were combined, and only unique systematic reviews and meta-analyses and policy/guidance documents for each trial were counted, 98% of these randomised controlled trials were cited by at least one review (mean 7.18 reviews per trial) and 68% by at least one policy/guidance document (mean 2.75 such documents per trial). The trend is for a decline in the mean number of citing secondary outputs per trial, but this is probably a function of publication date (see Figure 2).

Figure 2: Trends in total citation rates by year of publication in the HTA journal

Altmetric.com® identified a substantial minority of unique policy and guidance documents, which might not otherwise have been identified. For the HTA journal publications, 55 had at least one citing policy/guidance document; 31 were identified exclusively from the Science Citation Index; 15 exclusively from Altmetric.com®; and nine trials had relevant policy and guidance documents identified by both sources. Of the 106 pieces of policy/guidance identified for these 55 HTA journal trial publications, 28 were unique to Altmetric.com®. Of the

295 for the related publications, 40 were unique to Altmetric.com®. Altmetric.com® was particularly good at identifying relevant NICE guidance.

Quantitative content analysis

This in-depth analysis was performed on a subset of trials (n=68) purposively sampled from both the HTA journal publication and related journal publications that each had citation data from both systematic reviews/meta-analyses *and* policy/guidance documents (see the final column of Table 1). The integrated data for this subset are presented in Table 2.

<Table 2>

These 68 trials were cited in more than 300 reviews or meta-analyses and were found to be used in the synthesis more than 60% of the time. However, in 38% of these publications the trial and its data were not used in the synthesis at all. Rather the trial was cited only in the Introduction or Discussion or, in some cases, specifically in Cochrane reviews, the trial was cited in the list of excluded studies (failure to satisfy the inclusion criteria). These 68 trials were cited in 132 pieces of published policy/guidance, but in 59% of these publications the use of the trial and its data was symbolic only: they had no apparent influence on any recommendation or statement.

IV. DISCUSSION

Impact is a broad and complex topic involving multiple factors, which can and should be measured and captured in various ways[3,13,15], but it is certainly the case that simple citation metrics have limited value: there are significant differences even between medical disciplines and disease areas[26]. The work conducted here offers a simple, objective measure of the potential instrumental impact of a group of randomised controlled trials. The basic mean citation rate per trial (102.97) is impressive and compares extremely favourably with reported rates for medical and health sciences publications in this period (2006-2015) (mean normative citation rate reported as 33.63 per

publication for 2010)[27]. However, as noted above, a more useful citation metric is the number of times research is cited in a relevant and genuinely influential manner, i.e. an 'instrumental' citation. For randomised controlled trials, one should see their citation in policy documents and in systematic reviews/meta-analyses (specifically, the use of the trial and its data in a synthesis) as fulfilling such criteria.[3,15] The data reported here for citations within these types of documents are not nearly as impressive as the basic citation rate. However, for systematic reviews and meta-analyses they do suggest that, on average, each of these trials is cited by approximately seven systematic reviews or meta-analyses and its data are used in the synthesis in two thirds of them. While some trials achieved many such citations, and some none, others do reflect this division. For example, the 2009 VULCAN trial HTA journal publication[28] was cited by nine reviews: it was used in meta-analysis by two[29,30], narrative synthesis by three[31-33], was cited as an excluded study in a Cochrane review[34], and cited only in the Background[35,36] and Discussion[37] in the remaining three reviews.

These trials were also cited in far fewer policy and guidance documents than reviews, which reflects the general acceptance of the systematic review (of trials) as the gold standard for evidence-based decision-making[11]. There were certainly many cases where the influence of the trial and its data were clearly instrumental in shaping policy and recommendations both in the UK and internationally. For example, the TRAC trial[38] had a strong instrumental impact on the relevant NICE guideline: it was the most influential one of only two trials supporting a recommendation[39]. The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial[40] was cited as the single most instrumental piece of evidence in an American College of Cardiology/American Heart Association recommendation[41]. Such instrumental impact was also achieved by trials with findings of 'no effect', i.e. the intervention being tested was found to be no better, in terms of clinical effectiveness, than its comparator. For example, the SABRE trial[42] found that the intervention was no different from standard care and, as a result, recommendations were changed in Finnish guidance[43]. This is important because it demonstrates that 'positive' findings are not necessary for a trial to have instrumental impact. Indeed, it is noteworthy that 39/133 (29%) trials had such so-called 'negative' findings, and 27/39 of these were published in related journals also (see Supplementary file 1). The risk of publication bias is clearly much reduced when research is publicly-funded[44]. However, in the majority of cases (59%) instrumental influence on policy and guidance was difficult to discern or was clearly absent; the citation was 'symbolic' only. Nevertheless, these data indicate overall that these NIHR-

funded randomised controlled trials achieved impact both on the evidence-base most likely to inform policy decisions (systematic reviews) and on policy documents themselves.

Altmetric.com® was found to be a highly efficient means of identifying unique policy and guidance documents, such as NICE guidelines. Standard web searching, and even the search functions on relevant websites, e.g. the NICE website, does not permit the same efficient identification of potential policy documents. Key organisations like NICE are searched by Altmetric.com® for policy mentions, but their list is not exhaustive. As more national guidance centres and policy documents are added to the Altmetric.com® database, more useful altmetric insights will be made regarding how research is cited within national and international policy. These altmetrics will rely on research outputs being properly cited and linked within subsequent online policy documents.

Finally, the role played by the separate publication of NIHR-funded trials' key effectiveness findings in journals other than, and in addition to the HTA journal series is unclear. Superficially, these additional publications appear to generate larger numbers of basic citations, as well as comparatively higher citation rates for reviews and policy documents compared with their equivalent HTA journal publications (see Table 1). This is different from other findings in this area[45] and might demonstrate the value of publishing trial data in journals such as The Lancet and BMJ because they make the data more 'discoverable'. Alternatively, good quality systematic reviews and guidance documents would or should have found the HTA publication and its data anyway. Unfortunately, the data presented here do not allow us to compare citation rates for a particular trial directly across different journals, so it is not possible to reach an unequivocal conclusion on this matter[45].

Limitations

Citation data are evolving all the time and, since this analysis, each trial assessed here will have been cited on more occasions and potentially in more reviews and policy and guidance documents than reported here. These data therefore represent a particular point in time for these trials. It is also possible that a number of citing systematic reviews/meta-analyses and policy/guidance documents were missed by the searches conducted for this study, despite approaches that aimed at comprehensive coverage. However, this was a large sample of randomised

controlled trials from across a 10-year period, which therefore also took into account time lags and potential long-term impact[3], included substantial evidence from related publications, and used novel and efficient tools such as Altmetric.com® to identify otherwise difficult to discover citations. As a result, the chance of missing large numbers of reviews and policy documents that might affect the findings of this study in a meaningful way is low. The level of scrutiny required to determine levels of impact was substantial, so this is not a rapid form of assessment. However, the assessment of impact in terms of the use of these trials and their data in evidence synthesis and policy is both objective and meaningful. It is the exhaustive identification and quantitative content analysis of key publication and document types to understand impact on a deeper level that represents a real novel and meaningful extension to the existing body of research in this field. There is no reason why this approach and its principles should not apply to other types of health research also. Additional work might also consider time from a trial's publication to its citation in both reviews and policy documents, in order to understand this trajectory better. Finally, these trials were country-specific – they were all conducted in the UK - and this in turn might have limited their impact. However, as noted above (and as detailed in Supplementary file 1), the trials are not infrequently cited in the guidance or policy statements of non-UK countries.

V. CONCLUSIONS

The instrumental use of a randomised controlled trial in key secondary outputs (systematic reviews and meta-analyses, and policy and guidance documents) represents a single, easily quantifiable but important dimension of impact. This analysis has found that this 10-year sample of randomised controlled trials funded by the NIHR, and published in the HTA journal series (as well as their related publications in other journals), has impressive citation rates and a sizeable proportion are certainly being used in key publications in a genuinely instrumental manner.

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ABSTRACT:

OBJECTIVES:

Health Technology Assessment (HTA) aims to inform and support healthcare decision-making and trials are part of that process. The purpose of this study was to measure the impact of a sample of trials in a meaningful but robust fashion.

METHODS: All randomised controlled trials funded and published by the UK National Institute of Health Research (NIHR) in the Health Technology Assessment journals series and other peer-reviewed journals were identified for 2006-2015. Citation analysis was performed for all trials, and quantitative content analysis undertaken on a purposive sample to determine if impact could be categorised as 'instrumental', i.e. having a clear influence on key research and policy publications.

RESULTS:

The search identified 133 relevant trials. Citation rate per trial was 102.97. 129/133 (98%) of trials were cited in one or more systematic reviews or meta-analyses (mean per trial 7.18, range 0-44). Where they were cited, the trials were used in some form of synthesis 63% of the time. 91/133 (68%) of trials were found to be cited in one or more guidance or policy document (mean per trial 2.75, range 0-26), and had an instrumental influence 41% of the time. The publication of these trials' results in journals other than the Health Technology Assessment journal appears to enhance the discoverability of the trial data. Altmetric.com proved to be very useful in identifying unique policy and guidance documents.

CONCLUSION:

These trials have impressive citation rates and a sizeable proportion are certainly being used in key publications in a genuinely instrumental manner.

I. INTRODUCTION

Health Technology Assessment (HTA) aims to inform and support healthcare decision-making[1]. Randomised controlled trials are part of that process. They have an inherent value in that they provide an answer to a question where previously there had been uncertainty (equipoise). However, 'value' is a much-debated and multi-dimensional concept and a randomised controlled trial's value must extend beyond providing an answer to a question. It should have some demonstrable impact too[2]. However, assessing the impact of research presents many problems. First, there are many available models for doing so, but all have limitations[3,4]. Second, there is the definition of the term 'impact' itself. The measurement of impact can range from counting the number of times a piece of research is cited by others, to its generation of social, economic or health benefits beyond academia[3,5]. The former, the simple citation of research, is now recognised as a rather limited metric of either impact or quality[6,7]; it does not indicate how the research was used or its possible level of influence on other research[8]. The latter, the demonstration of benefits beyond academia, is undoubtedly more meaningful, but is also more difficult to determine. Consequently, there is potential value in examining not only those publications that are citing the research, but also how they are using it. In this way, it is possible to generate more meaningful data, while also exploring the broader impact of research.

This study aims to show that a particular approach to analysing citation data can provide greater insight into the impact of a particular body of research. In the payback framework of impact, a link is made between the primary and secondary outputs of research, in other words, between the original journal article and its use by other outputs.[3,9] In the case of randomised controlled trials, relevant secondary outputs include, most obviously, policy and guidance documents, but also systematic reviews and meta-analyses[10], which represent an influential form of evidence in the production of much policy and guidance[11,12,13]. Indeed, current published research on this topic has recognised that, 'there is merit in using existing systematic reviews to assess the impact of trials'[10] and that this knowledge gap remains to be filled. The trials funded by the UK National Institute of Health Research (NIHR) represent an obvious sample on which to conduct this work. This funder has previously sought to gauge the impact of the research it funds, for UK HTA projects generally, based on numbers of publications, basic citation analysis or a small number of individual case studies, testing authors' perceptions of the impact of their research[10,14]. This has included an evaluation of the use and weighting of some HTA trials in meta-analyses in Cochrane's reviews[10], but not their use in non-Cochrane reviews, other types of synthesis, or in policy or guidance documents. The aim of the present research is to extend this previous work by quantifying the impact of randomised controlled trials,

published in the NIHR Health Technology Assessment journal, based on the use of these trials in specific types of citing publication: systematic reviews and meta-analyses, and policy and guidance documents.

II. METHODS

Sample

This study is a citation analysis, with quantitative content analysis, of a sample of randomised controlled trials published in the NIHR Health Technology Assessment (HTA) journal. The HTA monograph is a peer-reviewed, open-access journal. Each issue is dedicated to a single project, such as a randomised controlled trial. To be included in the sample for this analysis, the publication had to be a randomised controlled trial funded by the UK NIHR and published in the HTA journal series from 2006 to 2015. A 10-year period of publications was chosen to enable the creation of a sizeable sample with substantial citation data; this would minimise the chance of findings being heavily skewed by results from a single year or a small group of atypical publications, and also controlled for potential long-term impact[3]. The date limit of 2015 permitted sufficient time for included trials to have generated citations up to the point of this analysis. To identify these trials, a search was conducted in MEDLINE, which fully indexes the HTA journal, for randomised controlled trials on any topic published in the HTA journal series from 2006 to 2015 inclusive. The results were then screened using the inclusion criteria described above and the following publication types were excluded: pilot, exploratory or feasibility trials; and studies evaluating methods of recruitment to trials. The result was a sample of all randomised controlled trials published in this journal series for a 10-year period. HTA journal publications contain the full report of each trial. This might include not only the trial's effectiveness findings, but also an economic evaluation and, in some cases, additional but related work, such as a qualitative study. These separate elements of the project might also be published in other peer-reviewed journals, which have more restrictive word-counts but also have the potential to increase the visibility and discoverability of the research[14]. In order to gain a fuller picture of the impact of this set of HTA journal trials, these related publications (effectiveness / efficacy results only) were also included in our sample. These additional, related publications were identified from a combination of sources: first, the trials' project webpages hosted by NIHR; and second, a search in the Science Citation Index (Web of Science).

Citation analysis

Citation analysis represents a conventional and robust approach to gauging a type of research impact. This approach tends to focus on a single funder; uses a single type of research project (e.g. trials) as the unit of analysis; and applies 'forward tracing' (identifying publications that cite the index publication)'[15]. In this case, the aim was to identify publications or documents that cited each HTA journal trial publication. To do this, a search was conducted in September and October 2018 in the Science Citation Index (Web of Science) to identify publications citing the HTA journal trials in our sample. This database was used because it is a highly comprehensive citation index and facilitates searching and downloading of results. The following citation data were then extracted for each HTA journal trial publication, as well as each related journal publication, and entered into Excel spreadsheets (see Supplementary file 1): total number of citations per trial; number of unique Cochrane and non-Cochrane systematic reviews and meta-analyses citing each trial; number of unique policy, practice or guidance documents or publications citing each trial. The two sets of data for the HTA journal publication and any related publication were then integrated (counting only once any systematic reviews and policy documents that cited both the HTA and its related publication). The 'policy' publications included any document described as guidance, guidelines, recommendations, position or consensus statements, or similar publication from national bodies, e.g. National Institute of Health and Care Excellence (NICE), or named specialist society, college or association (e.g. European Society of Cardiology, American College of Gastroenterology or the British Thoracic Society). This is not to claim equivalence between the potential impact of guidelines produced by national bodies, such as NICE, and specialist societies, but rather the aim was to capture the meaningful uptake of the trial evidence within different types and levels of publications that have the greatest potential to impact actual practice. Given that such policy and guidance documents can be difficult to find and many will not be catalogued in standard databases, a complementary search was conducted for each trial using the policy score facility of Altmetric.com®, which identifies web-based policy and related documents[16]. Altmetrics are alternative indicators of interest relating to scholarly outputs, most notably journal publications. Altmetric.com® are one of the pioneers in the use of altmetrics to provide useful insights into how a piece of research is communicated across the Web, primarily on traditional and social media platforms. In 2014 Altmetric.com® started searching for policy document mentions of research on the web, given such evidence was not indexed in traditional research databases. Altmetric.com® does this by tracking a broad range of policy sources directly from organisational websites. This is not an exhaustive list of policy documents but is updated when new policy sources are identified by Altemtric.com® or their users[17]. The policy documents within those websites are then searched for citations of research papers via

unique IDs, link searching and text mining. The complete citation data collected were tabulated and descriptive statistics were produced.

Quantitative content analysis

The citation analysis provided data on how often each trial had been cited overall, and how often by relevant 'secondary outputs', i.e. systematic reviews/meta-analyses, and policy or guidance documents. However, this is a limited metric; as noted above, it does not indicate how the research was used or its possible level of influence on other publications[8]. Greater scrutiny of the citation was therefore required. To do this, quantitative content analysis[18] was conducted on a subset of the total sample in order to determine how these trial publications were actually being used in these two subsets of relevant secondary outputs[8,19]. All included trials were sampled purposively to select those with extensive, relevant citation data across both types of secondary outputs. This sample was therefore composed of all HTA journal trial publications cited in at least one systematic review *and* at least one policy document, supplemented by related publications in other journals satisfying the same criteria but where the trial was not already identified from the HTA journal publication set. The aim was to compile an extensive and useful set of data for in-depth analysis, representing at least 50% of the whole 10-year sample, in order to test how these trials were actually used within relevant publication types.

In the quantitative content analysis, the impact of each published trial on the citing systematic review, policy or guidance document was categorised as either 'instrumental' or 'symbolic'. This terminology is commonly used in the research and policy impact literature[3,15]. Instrumental use refers to 'the explicit application of research to address a policy problem; where research influences issue identification, policy refinement, definition or implementation in a direct and potentially measurable way … that is, policymakers are aware that they are using research in this way and there may be evidence supporting claimed instances of use'[14]. Symbolic use of a piece of research is when it has been used 'to justify a position or specific action already taken for other reasons or to obtain specific goals based on a predetermined position'[14]. In previous studies, the vast majority of citations analysed have been found to be 'symbolic', that is, a 'reference in passing', providing only the most general support for a chosen approach, rather than representing anything more meaningful[3,19]. In this study, to be categorised as 'instrumental' impact in policy or guidance documents, the trial had to have clear supportive link to a recommendation or statement: it had to be one of only a small number of studies (1, 2, 3 or 4) supporting a recommendation. If this level of influence was not apparent, or the trial reported a finding different from the

recommendation, then the trial's citation was categorised as 'symbolic' for that piece of guidance. Applying the same principles to citing systematic reviews/meta-analyses, the trial had to be used in the actual synthesis to be categorised as having an 'instrumental' impact, otherwise its impact was categorised as 'symbolic' only.

III. RESULTS

The total number of NIHR-funded randomised controlled trials published in the HTA journal series for the 10 years between 2006 and 2015 was n=133. These were all clinical effectiveness or diagnostic accuracy randomised controlled trials, 40 of which were described as pragmatic randomised controlled trials. 119 trials also included a cost-effectiveness analysis or other economic evaluation. Additional elements reported in the HTA journal publications related to the trials in this sample were qualitative (n=20) and observational studies (n=9). Two trials experienced recruitment problems[20,21], although both had citation data. Related publications reported the effectiveness results of 82 of these 133 trials in journals other than the HTA journal series. A typical example is provided by the COMICE trial, the effectiveness results of which were published in both the HTA journal[22,23]and The Lancet[19]. There has been a marked increase in the numbers of trials published over this period, although with the odd exception the proportion of trials with both an HTA and related but separate publication has remained fairly stable (Figure 1).

Figure 1: Numbers of HTA journal trials and numbers with key related publications by year of publication in the HTA journal

Citation analysis

The citation data are presented in Table 1 (the complete data sheet is available as Supplementary file 1). The basic mean citation rate per trial was approximately 103. Across both the HTA and related publications, 131/133 (98%) of the trials were cited in either a systematic review or meta-analysis, or in a policy or guidance document; only two trials (2%) were not found in this analysis to be cited in any potentially relevant document[24-25]. 129/133 (97%) trials were found to be cited in one or more systematic reviews or meta-analyses, the vast majority of which were non-Cochrane reviews (84%). 91/133 (68%) of trials were found to be cited in one or more documents of guidance

or policy. The number of citing systematic reviews and meta-analyses per trial ranged from 0 to 44, and policy and guidance documents per trial from 0 to 26.

<Table 1>

The publication of trials' effectiveness findings in journals other than the HTA journal has a clear influence on the citation metrics. These related publications achieve twice the mean number of citing reviews and more than four times the mean number of citing policy/guidance documents than the HTA journal publication: 125 vs 25 citations per trial; 7.16 vs 3.32 reviews per trial; 3.59 vs 0.80 policy/guidance documents per trial (Table 1). This is important because the original 82 HTA journal publications for these 82 related publications reflected the mean rates for the 133 HTA journal publication sample as a whole: means of 25.95 vs 25.36 citations, 3.55 vs 3.32 reviews, 0.80 vs 0.80 policy/guidance documents. Sixty-six systematic reviews/meta-analyses and 29 policy/guidance documents cited both the HTA journal publication and the related publication. When the data from both the HTA journal and their related publications were combined, and only unique systematic reviews and meta-analyses and policy/guidance documents for each trial were counted, 98% of these randomised controlled trials were cited by at least one review (mean 7.18 reviews per trial) and 68% by at least one policy/guidance document (mean 2.75 such documents per trial). The trend is for a decline in the mean number of citing secondary outputs per trial, but this is probably a function of publication date (see Figure 2).

Figure 2: Trends in total citation rates by year of publication in the HTA journal

Altmetric.com® identified a substantial minority of unique policy and guidance documents, which might not otherwise have been identified. For the HTA journal publications, 55 had at least one citing policy/guidance document; 31 were identified exclusively from the Science Citation Index; 15 exclusively from Altmetric.com®; and nine trials had relevant policy and guidance documents identified by both sources. Of the 106 pieces of policy/guidance identified for these 55 HTA journal trial publications, 28 were unique to Altmetric.com®. Of the

295 for the related publications, 40 were unique to Altmetric.com®. Altmetric.com® was particularly good at identifying relevant NICE guidance.

Quantitative content analysis

This in-depth analysis was performed on a subset of trials (n=68) purposively sampled from both the HTA journal publication and related journal publications that each had citation data from both systematic reviews/meta-analyses *and* policy/guidance documents (see the final column of Table 1). The integrated data for this subset are presented in Table 2.

<Table 2>

These 68 trials were cited in more than 300 reviews or meta-analyses and were found to be used in the synthesis more than 60% of the time. However, in 38% of these publications the trial and its data were not used in the synthesis at all. Rather the trial was cited only in the Introduction or Discussion or, in some cases, specifically in Cochrane reviews, the trial was cited in the list of excluded studies (failure to satisfy the inclusion criteria). These 68 trials were cited in 132 pieces of published policy/guidance, but in 59% of these publications the use of the trial and its data was symbolic only: they had no apparent influence on any recommendation or statement.

IV. DISCUSSION

Impact is a broad and complex topic involving multiple factors, which can and should be measured and captured in various ways[3,13,15], but it is certainly the case that simple citation metrics have limited value: there are significant differences even between medical disciplines and disease areas[26]. The work conducted here offers a simple, objective measure of the potential instrumental impact of a group of randomised controlled trials. The basic mean citation rate per trial (102.97) is impressive and compares extremely favourably with reported rates for medical and health sciences publications in this period (2006-2015) (mean normative citation rate reported as 33.63 per

publication for 2010)[27]. However, as noted above, a more useful citation metric is the number of times research is cited in a relevant and genuinely influential manner, i.e. an 'instrumental' citation. For randomised controlled trials, one should see their citation in policy documents and in systematic reviews/meta-analyses (specifically, the use of the trial and its data in a synthesis) as fulfilling such criteria.[3,15] The data reported here for citations within these types of documents are not nearly as impressive as the basic citation rate. However, for systematic reviews and meta-analyses they do suggest that, on average, each of these trials is cited by approximately seven systematic reviews or meta-analyses and its data are used in the synthesis in two thirds of them. While some trials achieved many such citations, and some none, others do reflect this division. For example, the 2009 VULCAN trial HTA journal publication[28] was cited by nine reviews: it was used in meta-analysis by two[29,30], narrative synthesis by three[31-33], was cited as an excluded study in a Cochrane review[34], and cited only in the Background[35,36] and Discussion[37] in the remaining three reviews.

These trials were also cited in far fewer policy and guidance documents than reviews, which reflects the general acceptance of the systematic review (of trials) as the gold standard for evidence-based decision-making[11]. There were certainly many cases where the influence of the trial and its data were clearly instrumental in shaping policy and recommendations both in the UK and internationally. For example, the TRAC trial[38] had a strong instrumental impact on the relevant NICE guideline: it was the most influential one of only two trials supporting a recommendation[39]. The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial[40] was cited as the single most instrumental piece of evidence in an American College of Cardiology/American Heart Association recommendation[41]. Such instrumental impact was also achieved by trials with findings of 'no effect', i.e. the intervention being tested was found to be no better, in terms of clinical effectiveness, than its comparator. For example, the SABRE trial[42] found that the intervention was no different from standard care and, as a result, recommendations were changed in Finnish guidance[43]. This is important because it demonstrates that 'positive' findings are not necessary for a trial to have instrumental impact. Indeed, it is noteworthy that 39/133 (29%) trials had such so-called 'negative' findings, and 27/39 of these were published in related journals also (see Supplementary file 1). The risk of publication bias is clearly much reduced when research is publicly-funded[44]. However, in the majority of cases (59%) instrumental influence on policy and guidance was difficult to discern or was clearly absent; the citation was 'symbolic' only. Nevertheless, these data indicate overall that these NIHR-

funded randomised controlled trials achieved impact both on the evidence-base most likely to inform policy decisions (systematic reviews) and on policy documents themselves.

Altmetric.com® was found to be a highly efficient means of identifying unique policy and guidance documents, such as NICE guidelines. Standard web searching, and even the search functions on relevant websites, e.g. the NICE website, does not permit the same efficient identification of potential policy documents. Key organisations like NICE are searched by Altmetric.com® for policy mentions, but their list is not exhaustive. As more national guidance centres and policy documents are added to the Altmetric.com® database, more useful altmetric insights will be made regarding how research is cited within national and international policy. These altmetrics will rely on research outputs being properly cited and linked within subsequent online policy documents.

Finally, the role played by the separate publication of NIHR-funded trials' key effectiveness findings in journals other than, and in addition to the HTA journal series is unclear. Superficially, these additional publications appear to generate larger numbers of basic citations, as well as comparatively higher citation rates for reviews and policy documents compared with their equivalent HTA journal publications (see Table 1). This is different from other findings in this area[45] and might demonstrate the value of publishing trial data in journals such as The Lancet and BMJ because they make the data more 'discoverable'. Alternatively, good quality systematic reviews and guidance documents would or should have found the HTA publication and its data anyway. Unfortunately, the data presented here do not allow us to compare citation rates for a particular trial directly across different journals, so it is not possible to reach an unequivocal conclusion on this matter[45].

Limitations

Citation data are evolving all the time and, since this analysis, each trial assessed here will have been cited on more occasions and potentially in more reviews and policy and guidance documents than reported here. These data therefore represent a particular point in time for these trials. It is also possible that a number of citing systematic reviews/meta-analyses and policy/guidance documents were missed by the searches conducted for this study, despite approaches that aimed at comprehensive coverage. However, this was a large sample of randomised

controlled trials from across a 10-year period, which therefore also took into account time lags and potential long-term impact[3], included substantial evidence from related publications, and used novel and efficient tools such as Altmetric.com® to identify otherwise difficult to discover citations. As a result, the chance of missing large numbers of reviews and policy documents that might affect the findings of this study in a meaningful way is low. The level of scrutiny required to determine levels of impact was substantial, so this is not a rapid form of assessment. However, the assessment of impact in terms of the use of these trials and their data in evidence synthesis and policy is both objective and meaningful. It is the exhaustive identification and quantitative content analysis of key publication and document types to understand impact on a deeper level that represents a real novel and meaningful extension to the existing body of research in this field. There is no reason why this approach and its principles should not apply to other types of health research also. Additional work might also consider time from a trial's publication to its citation in both reviews and policy documents, in order to understand this trajectory better. Finally, these trials were country-specific – they were all conducted in the UK - and this in turn might have limited their impact. However, as noted above (and as detailed in Supplementary file 1), the trials are not infrequently cited in the guidance or policy statements of non-UK countries.

V. CONCLUSIONS

The instrumental use of a randomised controlled trial in key secondary outputs (systematic reviews and meta-analyses, and policy and guidance documents) represents a single, easily quantifiable but important dimension of impact. This analysis has found that this 10-year sample of randomised controlled trials funded by the NIHR, and published in the HTA journal series (as well as their related publications in other journals), has impressive citation rates and a sizeable proportion are certainly being used in key publications in a genuinely instrumental manner.

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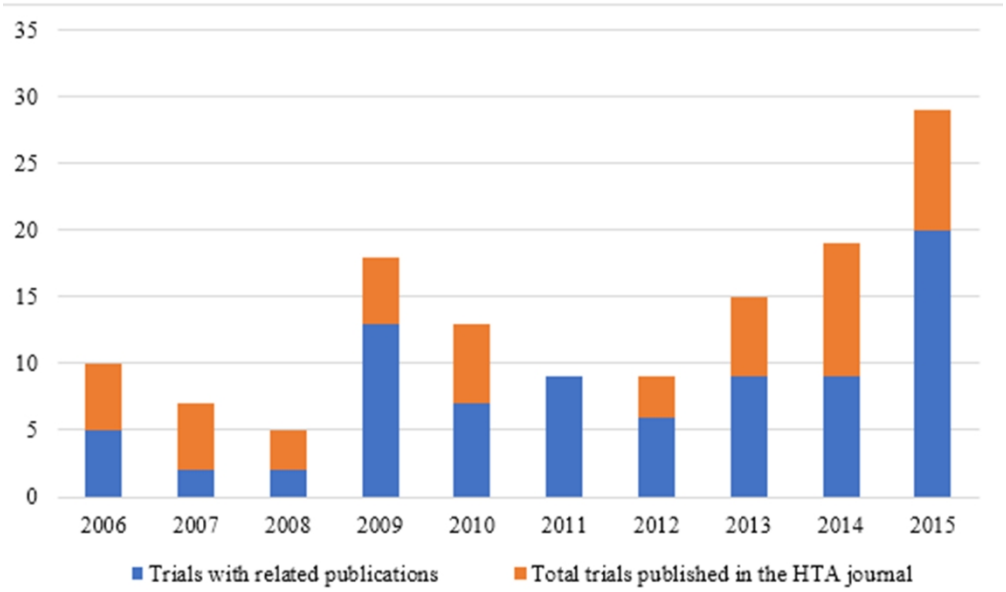

Figure 1: Numbers of HTA journal trials and numbers with key related publications by year of publication in the HTA journal

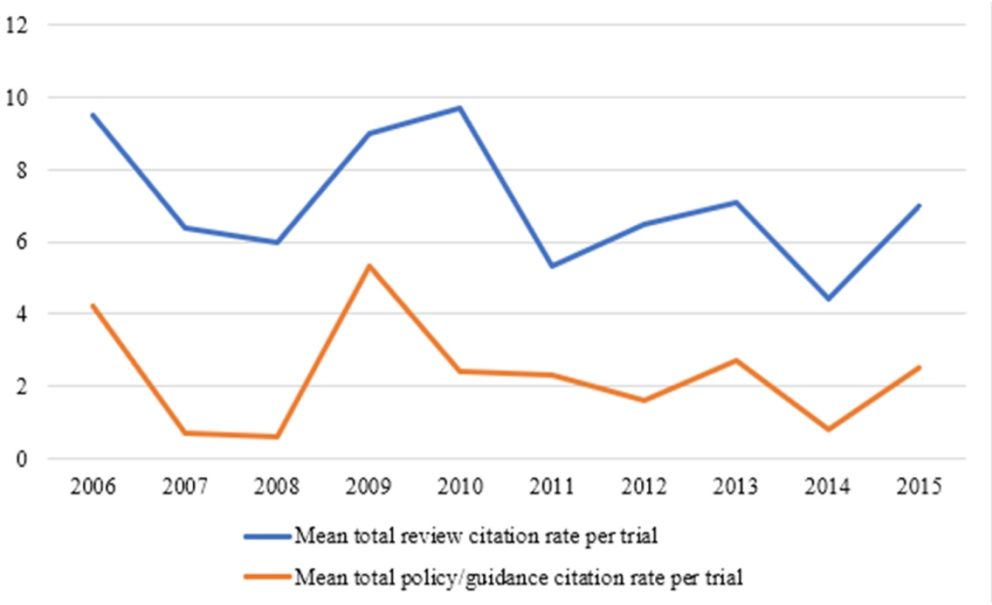

Figure 2: Trends in total citation rates by year of publication in the HTA journal

Table 1: Citation data for trials from HTA journal publications and related publications

Trials	Total citations	Mean (range) per trial	Trials cited by ≥1 review Total n=	Percentage of Cochrane reviews Total n=	Percentage of Non-Cochrane reviews Total n=	Mean (range) per trial		Trials cited by ≥1 policy documents Total n=	Mean number of policy documents per trial	Trials with ≥1 systematic review and ≥1 policy documents Total n=
HTA journal										
133	3373	25.36 (1-106)	117/133 (88%) n=441	19% n=84	81% n=357	3.32 (0-12)		55/133 (41%) n=106	0.80 (0-6)	49
HTA publications with related publications in other journals (one per trial)										
82	10322	125.88 (1-1286)	76/82 (93%) n=587	16% n=92	84% n=495	7.16 (0-34)		68/82 (83%) n=294	3.59 (0-26)	19

Trials	Total citations	Mean (range) per trial	Trials cited by ≥1 review Total n=	Percentage of Cochrane reviews Total n=	Percentage of Non-Cochrane reviews Total n=	Mean (range) per trial		Trials cited by ≥1 policy documents Total n=	Mean number of policy documents per trial	Trials with ≥1 systematic review and ≥1 policy documents Total n=
Total across all publications (HTA journal publication and any related publications: 216 publications relating to 134 trials)										
†	*13695	102.97 (1-1286)	129/133 (98%) n=962	16% n=156	84% n=806	7.18 (0-44)		91/133 (68%) n=374	2.75 (0-26)	68

*Includes double-counting of publications that cite both the HTA and the related publication †Figures reported here are numbers of unique reviews and policy/guidance documents

Table 2: Use of trials published in the HTA journal, and related publications, in reviews and policy documents

Trials	Number of unique citing reviews	Used in meta-analysis or network meta-analysis	Used in narrative synthesis	Not used in synthesis		Number of unique citing policy documents	Instrumental	Symbolic
HTA journal								
49	208	53 (25%)	82 (39%)	73 (35%)		88	38 (43%)	50 (57%)
Related publications in other journals								
19	104	40 (38%)	20 (19%)	44 (42%)		44	16 (36%)	28 (64%)
Totals across all publications								
68	312	93 (30%)	102 (33%)	117 (38%)		132	54 (41%)	78 (59%)

Responses to reviewers

Reviewer 1	Response
A concept map of impact and value would communicate the researcher's intended meaning for the interrelationship of these with HTAs, and the NIHR.	We have not made this revision as we are not entirely sure what is being proposed by the reviewer, especially as all reference to 'value' was removed from the manuscript in the previous revision (except for two sentences early in the Introduction).
As therapy area/medical specialty also influences the quantity and quality of citation (e.g. cardiology-related HTAs would get more citations than a radiology-related HTA), there should be a way of controlling/adjusting for this. Perhaps a field specific sensitivity analysis?	We agree that this is an interesting idea: to analyse the relative citation rates for distinct specialities. However, there is no universally-accepted list of medical specialities. We conducted a pilot categorisation on the 29 trials published in 2015 using the UK Medical Schools Council's list of medical specialities. The potential categories for this sample of trials were: Medicine (n=13); Psychiatry (n=4); Surgery (n=3); General Practice (n=3); Public Health (n=2); Clinical Oncology (n=1); Clinical Radiology (n=1); Paediatrics (n=1). These specialities are quite broad – arguably too broad to be informative. The 13 trials categorised under Medicine could be further categorised by a range of sub-specialities, including cardiology, genitourinary medicine, geriatrics, pharmaceutical medicine, renal medicine, respiratory medicine, and stroke medicine. The specialities of Surgery and Psychiatry could be equally sub-divided. If this was conducted for the whole sample, the result would be a large number of (sub)specialities, each with between only 1 and 5 trials, for which citation numbers would then be extracted from the Supplementary file. Given that many would have only 1 or 2 trials, it would not be possible to infer any meaningful comparative data regarding the relative 'impact' of trials of different specialities. As a result, we hope that you agree that this proposed analysis and revision need not be conducted.
Is the NIHR's remit for a specific country a potential limiting factor in its impact? Country-specific audience may also play a role in quantifying the influence of a publication on policies	This is an interesting point, thank you, and related text has now been added to the Limitations, p.11.
Time from publication to citation would also be a useful metric, particularly since the study looked at a slice of studies from 2006 to 2015. The impact of published studies may be time-sensitive as well.	We agree that this would be interesting, but would require substantial additional work to identify the first review and the first policy citation for each of the 133 trials (even just for the HTA journal publication alone). This cannot be completed in the time available for this revision. As a result, we have added a comment about this metric in the Limitations, p.11.
Reviewer 2	
Well done, the amended version is much improved.	No action needed

https://docs.google.com/spreadsheets/d/14VLaDgju84Aq5QntGt4PK7pi7pycmHmA/edit#gid=166818731