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# Intervention development and treatment success in UK Health Technology Assessment funded trials of rehabilitation: a mixed methods analysis



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| | |

# Intervention development and treatment success in UK Health Technology Assessment funded trials of rehabilitation: a mixed methods analysis

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**Keywords**

Rehabilitation, randomised controlled trials, quality, intervention development, mixed methods

**Abstract**

**Objectives:** Rehabilitation is a complex process and trials of rehabilitation interventions are increasing in number. This study aimed to establish treatment success rates in rehabilitation trials funded by the NIHR Health Technology Assessment (HTA) programme and examine any relationship between treatment success and the quality of intervention development work undertaken.

**Design:** Mixed methods study

**Setting:** UK

**Methods:**

The NIHR HTA portfolio was searched for all completed definitive randomised controlled trials of physiotherapy, occupational therapy or speech and language therapy from inception to July 2016. Treatment success was categorised according to criteria developed by Djulbegovic and colleagues. Detailed textual data regarding any intervention development work were extracted from the trial reports and supporting publications and informed the development of a quality rating. Mixed methods integrative analysis was undertaken to explore the relationship between the quantitative and qualitative data using joint displays.

**Results:** Fifteen trials were included in the review. Of these, five reported a definitive finding, four of which were in favour of the 'new' intervention. Eight trials reported a true negative (no difference) outcome. Integrative analysis indicated those with lower quality intervention development work were less likely to report treatment success, although some older and possibly less well reported trials reported effective interventions.

**Conclusions:** Despite much effort and funding, most rehabilitation trials report equivocal findings. Greater focus on high quality intervention development may reduce the likelihood of a null result in the definitive trial.

**Strengths and limitations of this study:**

- The use of mixed methods integrative analyses to explore the relationship between quality of intervention development work and treatment success.
- The study comprised randomised controlled trials of rehabilitation from a single UK funder.
- Factors other than intervention development can influence treatment success

## BACKGROUND

Rehabilitation is *"a set of interventions designed to optimise function and reduce disability in individuals with health conditions in interaction with their environment".*[1] and is an essential aspect of healthcare provision. By its very nature rehabilitation in clinical practice is an individually focused, complex activity, involving interventions that are multi-faceted and often implicit in nature[2] and as such, historically, this has been viewed as a barrier to undertaking research.[3] This said, there is a growing body of evidence from randomised controlled trials of rehabilitation, suggesting that these challenges can be overcome.[4] This may, in part, be supported by the publication of the MRC Framework for developing and evaluating complex interventions.[5 6]

The framework was developed to optimise the likelihood that new interventions are not rejected as being ineffective when inadequate effort has been made in the development of the intervention.[7] Likewise, Chalmers and Glasziou[8] highlighted the importance of avoiding research waste and recommended that sufficient effort is made to ensure the relevant research questions are identified and addressed using high quality research methods. However, there appears to have been no formal evaluation of the impact of using the development component of the framework on trial outcomes and whether we are observing evidence of effective interventions being developed.

Previous UK[9] and USA[10] reviews synthesised successful and non-successful treatment outcomes from trials of new interventions in order to assess the equipoise principle and to understand what return has been achieved on the investment made by those taking part in the trials, researchers and funders. Dent and Raftery[9] reported 24% (20/85) primary outcome comparisons as having a positive result, of which 16/85 (19%) were in favour of the new intervention, with 19/85 (22%) comparisons reporting a true negative outcome. However, these authors did not focus on rehabilitation interventions, nor did they seek to understand factors that may impact on treatment success, such as the quality or intensity of intervention development pre-trial procedures. In order to build on the work of Dent and Raftery,[9] who evaluated the outcomes of UK National Institute of Health Research (NIHR) Health Technology Assessment (HTA) funded research, we aimed to use data,[11] from the same funding stream to: (1) establish the treatment outcomes of NIHR HTA funded randomised controlled trials of physiotherapy, occupational therapy and speech and language therapy using Djulbegovic's classification[10]; (2) establish how many new interventions were found to be effective; (3) examine what work had been done in terms of developing the new intervention; and (4) examine the relationship between (1) and (3). We adopted a mixed methods approach to address the study aims. Although evidence of using integrative mixed methods approaches in synthesising evidence on complex interventions is limited, mixing together qualitative and quantitative data can generate understanding that has the potential to be greater than the sum of the individual parts.[12]

## METHODS

### Design

We undertook a review of NIHR HTA funded randomised controlled trials of rehabilitation interventions using narrative synthesis of outcomes and mixed methods analysis of the relationship between intervention development and categorical treatment outcomes using joint displays.

#### *Data sources and inclusion criteria*

We included superiority randomised controlled trials of physiotherapy, occupational therapy, or speech and language therapy funded by the NIHR HTA programme. The NIHR HTA programme is the leading public funding source for randomised controlled trials (RCTs) in the UK and trials of rehabilitation are increasingly part of the portfolio. We only included completed RCTs whose main trial findings were reported in an HTA monograph or peer-reviewed publication. We excluded pilot or feasibility RCTs and systematic reviews, along with studies where the interventions were primarily psychological or cognitive, those where it was unclear which study arm was the control, where there was a lack of a clear primary outcome (including primary time point) or where the primary outcome findings were not reported with a 95% confidence interval.

***Search and screening***

We searched the HTA Project Portfolio (since superseded by the NIHR Journals Library) from inception to July 2016 using the following keywords: physiotherap*, occupational therap*, speech and language therap* and rehabilitation. We removed duplicates and then titles and scientific abstracts were reviewed for potential inclusion by one person and checked by a second. Subsequently full text reports were screened for inclusion by one person and checked by a second. Any disagreements were discussed and agreed with a third person.

***Data extraction***

All data were extracted by one person and checked by a second. Discrepancies were discussed and resolved with a third person.

*Trial data:* Data extracted from each trial publication included trial design, target population, primary outcome(s) and time point, minimal important clinical difference (MCID) that the trial aimed to detect, planned and achieved sample size, and primary outcome results with 95% CI. We also recorded the professional background of the Chief Investigator and amount of funding awarded.

*Intervention development data*: Using the revised version of Criteria for Reporting the Development and Evaluation of Complex Interventions (CReDECI 2)[13] and the Template for Intervention Description and Replication checklist (TIDieR)[14] as frameworks we extracted all available documentary (qualitative) data from the body of the text regarding intervention development, including descriptions of underlying theory, intervention components and reasons for selection, intended interactions between components, contextual considerations, piloting of intervention and impact of definitive intervention to be evaluated, control components, planned intervention delivery and materials. Where additional supporting publications were cited, such as a protocol or intervention development studies, we used these as additional sources of documentary data.

**Data analysis**

We used summary statistics to describe the characteristics of the included studies. We categorised primary outcome findings into one of six treatment outcome categories as described by Djulbegovic and colleagues,[10] these being: 1) statistically significant in favour of the new treatment, 2) statistically significant in favour of the control treatment 3) true negative, 4) truly inconclusive, 5) inconclusive in favour of new treatment or 6) inconclusive in favour of the control treatment. This was achieved by comparing the 95% confidence interval for the difference in primary outcome to the difference specified in the sample size calculation.[9] If the 95% confidence interval excluded a

meaningful difference in either direction, implying the treatments have similar effects, the results were categorised as true negative. If the 95% confidence interval included a meaningful difference in either direction (i.e. trial failed to answer the primary question), the results were categorised as being truly inconclusive.

Where a single primary outcome and primary time point were not explicitly identified we utilised the following hierarchy to determine which primary outcome would be used in the analysis:

- Explicitly defined primary outcome
- Outcome used in power calculation
- Main outcome stated in trial objectives
- First outcome reported in sample size calculation

If a primary time point was not reported we used the first follow up time point as this is when we would expect the intervention to have had the greatest effect.

Our preliminary analysis of the qualitative documentary data involved the reading and re-reading of source documents and the extracted descriptions to consolidate our understanding of the development work undertaken in each study. Using a reflective and iterative process we undertook thematic analysis to distil, structure and make sense of intervention development activity by coding and organising data into themes and subthemes. Each theme and sub-theme provided a coherent description of the development work undertaken for each study, which were then synthesised into short descriptors to allow us to produce summary tables. The summary tables comprised a row for each study with columns for each theme and, where relevant, each subtheme. A second researcher checked, discussed and refined descriptors to ensure accuracy. From these descriptions we then developed descriptive ratings on the quality of the intervention development. Depending on the nature of the data, ratings were categorised and the iterative process involved two researchers refining and checking ratings to ensure they reflected the summary data from each study. Table 1 also provides examples of summary data underpinning each rating. In order to provide a visual representation of the quality of intervention development work these ratings were then converted to a quality coding to indicate high quality, some or unclear quality or limited quality.

To examine the relationship between intervention development and treatment success, we applied mixed methods analytical techniques in novel ways. For each study, we combined ratings derived from the qualitative data on intervention development with the quantitative data on treatment outcomes in a joint display.

## RESULTS

We included 15 studies (Figure 1), with a combined sample size of 9035 participants, 7834 of whom provided primary outcomes data. Five primary outcomes were symptom-based or clinical outcomes, seven were functional measures, two were combined measures and one assessed quality of life. Primary time points varied from immediately post-intervention to one year (median 6 months). All but one of the trials were individually randomised. Thirteen of the studies utilised a two-arm, parallel RCT design, one used a four-arm factorial design of which only two arms related to physical

rehabilitation, and one was a two-arm cluster RCT. The study populations were: Stroke (n=4), Neurological conditions (n=2), Inflammatory/Immune system disorders (n=2) and one each of Respiratory, Musculoskeletal, Cardiovascular, Mental Health, Accident/injuries, Renal/urogenital and other. Nine interventions were of physiotherapy, two occupational therapy, one speech and language therapy, one of multiple professions both delivering the intervention and two where different professions delivered the intervention, for example, a physiotherapist or an occupational therapist. The Chief Investigators leading the studies were physicians (n=7), physiotherapists (n=5), occupational therapists (n=1), psychologists (n=1) and methodologists (n=1). The total amount of research funding awarded was £11,361,182.

One third of studies (5/15) reported a definitive finding in favour of one of the treatment arms - four studies in favour of the new treatment, one in favour of the control. Of those with negative results, eight studies reported a true negative (no difference) outcome, one was inconclusive in favour of the new treatment, and one inconclusive in favour of the control treatment (Figures 2 and 3).

Qualitative data informed two themes and ten sub-themes which enabled us to develop data-driven quality ratings (Table 1):

1. *Preparatory work* (Need for the study, underpinning theory for the intervention, co-design, context considerations and intervention piloting)
2. *Intervention and control* (Intervention content and dose, individual tailoring, adherence strategies, standardised training, control content and dose)

Table 2 presents the integrative analysis using a joint display. No single study was deemed to be high quality in each sub-theme. The best rated studies did not achieved the highest quality rating in only one area – co-design. These studies reported only expert clinical input into co-designing the intervention with a lack of clear patient and public involvement, however, two of them reported a definitive trial outcome in favour of the new intervention. There does not appear to be a single aspect of intervention development driving study outcomes. This said, those with lower quality development work appear more likely to show no difference in outcomes compared with those with higher quality development work. Some areas of intervention development appear to be improving with time, these being articulating a clear need and theoretical underpinning, co-design, piloting and descriptions of intervention and control components.

Table 1 Description of themes, subthemes and quality ratings with examples

| Theme | Sub-theme | Description of rating | Examples of data supporting rating | Rating |
|---|---|---|---|---|
| **Preparatory work** | **Need for the study** | Multiple sources of evidence of need for the study e.g. recent systematic review, guidelines, high level reports, commissioned research, national audit | International task force highlighted lack of evidence and need for evaluation. Cochrane review drew similar conclusions. | ▲ |
| | | Single source of evidence / non-systematic review to support need for study | Old systematic review indicates paucity of high quality research. | ■ |
| | | Lack of clarity or underpinning evidence regarding need for study | Poor justification for the study. Evidence cited doesn't support the need for this particular study. | ● |
| | **Theoretical underpinning** | Theoretical underpinning described | Physiological and psychological theories underpinning the intervention described in detail. | ▲ |
| | | Lacks clear theoretical underpinning | No information provided regarding the theoretical basis for the intervention provided. | ■ |
| | **Co-design** | Good PPI and expert clinical input | Patients and clinicians helped develop the intervention. | ▲ |
| | | Good PPI but weak or no expert clinical input / Good clinical input but unclear or no PPI | Clinicians contributed to the intervention development but no indication of service user involvement. | ■ |
| | | No co-design | No co-design was undertaken to develop the intervention. | ● |
| | **Contextual considerations** | Context considered | The use of different professionals in delivering the intervention reflected the real world situation of how this would occur in practice. | ▲ |
| | | Context not adequately considered | There was a lack of understanding of relevant context and factors needed for intervention development and delivery. | ● |
| | **Piloting of intervention** | Pilot conducted, evaluated and findings addressed for main evaluation | The pilot data helped refine the intervention for evaluation in the main trial. | ▲ |
| | | Pilot conducted but findings not clearly addressed in intervention for main evaluation | The pilot work led to a modification of the control intervention but unclear as to whether this also happened for the novel intervention. | ■ |
| | | No pilot reported | No piloting of intervention reported | ● |

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| **Intervention and control** | **Content and dose** | Intervention components and dose clearly described | The content and the dose of the exercise programme was described in detail. | ▲ |
| | | Intervention components clearly described but dose was not standardised | The content of the programme was well described but no specific dose was prescribed. | ■ |
| | | Intervention not replicable from description of components and dose | Intervention was based on usual practice and had no protocol or guidance on minimum dose. | ● |
| | **Tailoring** | Formalised assessment to inform tailoring | An assessment tool was used to determine the individuals level of exercise intensity | ▲ |
| | | Clinical judgement only used to inform tailoring | Therapists used their clinical judgement to individually tailor programmes. | ■ |
| | | Not adequately reported | Intervention individually tailored but no information as to how this was undertaken. | ● |
| | **Adherence support strategies** | Explicit strategies to support adherence to the intervention clearly reported | Specific adherence strategies described as part of the intervention. | ▲ |
| | | No clear information regarding adherence support strategies | No information reported regarding adherence strategies. | ● |
| | | Supporting adherence is not relevant to the intervention | The intervention was passive and adherence strategies not relevant. | NA |
| | **Intervention training** | Standardised training in intervention received +/- additional/ongoing support or training | Staff attended a 1.5 day training session and had an additional support session with ongoing contact from research team. | ▲ |
| | | No standardised intervention training received but staff delivering described to be experienced in the intervention or training of staff unclear/not reported | Staff have post graduate training in the intervention but no study specific training reported. | ■ |
| | **Control description** | Active control/attention control/usual care with some standardised components | Control was an active intervention that differed from intervention only in terms of delivery setting. | ▲ |
| | | Usual care had no standardised components | Control was usual care and was not standardised between sites. | ■ |

Key: ▲ High quality ■ Some/Unclear quality ● Limited quality

Table 2 Joint display of the quality of intervention development work of NIHR funded trial of rehabilitation and treatment success

| Year of Publication | Need | Theory | Co-design | Context | Pilot | Intervention Content | Tailored | Adherence strategies | Training delivery | Control description | Treatment success |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2012 | ▲ | ▲ | ■ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | Statistically significant in favour of intervention |
| 2015 | ▲ | ▲ | ■ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | Statistically significant in favour of intervention |
| 2013 | ▲ | ▲ | ■ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | True negative (No difference) |
| 2011 | ▲ | ▲ | ▲ | ▲ | ● | ▲ | ▲ | ▲ | ▲ | ▲ | True negative (No difference) |
| 2014 | ▲ | ▲ | ▲ | ▲ | ■ | ■ | ▲ | ▲ | ▲ | ▲ | True negative (No difference) |
| 2012 | ▲ | ▲ | ■ | ▲ | ▲ | ■ | ▲ | ▲ | ■ | ▲ | Inconclusive in favour of intervention |
| 2015 | ▲ | ▲ | ● | ▲ | ■ | ▲ | ▲ | NA | ▲ | ■ | Statistically significant in favour of control |
| 2016 | ▲ | ▲ | ■ | ▲ | ■ | ● | ▲ | ▲ | ■ | ■ | True negative (No difference) |
| 2007 | ● | ▲ | ● | ▲ | ● | ▲ | ■ | ▲ | ▲ | ■ | True negative (No difference) |
| 2004 | ■ | ■ | ● | ▲ | ● | ▲ | ▲ | ■ | ■ | ▲ | Statistically significant in favour of intervention |
| 2010 | ▲ | ■ | ● | ● | ● | ▲ | ■ | ▲ | ■ | ▲ | True negative (No difference) |
| 2005 | ■ | ▲ | ■ | ● | ■ | ▲ | ■ | ■ | ■ | ▲ | Inconclusive in favour of control |
| 2016 | ● | ■ | ■ | ▲ | ● | ● | ▲ | ■ | ■ | ■ | True negative (No difference) |
| 2004 | ■ | ■ | ● | ▲ | ● | ● | ● | NA | ■ | ■ | Statistically significant in favour of intervention |
| 2007 | ● | ▲ | ● | ● | ● | ● | ● | ■ | ■ | ■ | True negative (No difference) |

Key:

▲ High quality ■ Some/Unclear quality ● Limited quality

## DISCUSSION

We found that only one third (5/15) of the randomised controlled trials of rehabilitation funded by the NIHR HTA programme successfully demonstrated a statistically significant effect for one of the randomised groups in each trial. Four (27%) trials found an effect in favour of the 'new' intervention. We were able to use contemporary research methods to develop an assessment of the quality of development work and assessed the included trials to be of varied quality in terms of intervention development work. In general, we found that those studies with better quality intervention development work were more likely to report treatment success, although older, possibly less well reported studies also reported effective interventions. We found that interventions that were less well developed were more likely to lead to results categorised as truly negative, i.e. which excluded a meaningful difference in outcome in either direction. Developments in complex intervention evaluation[5], reporting standards[14 15] and involving patients and the public in research[16] have occurred since the inception of the HTA programme and as such some development work may not have been reported in the included studies. There are of course other factors that influence trial findings, including trial conduct, however our question was specifically determined to explore what if any relationship existed between intervention development and outcomes and not in the effectiveness of particular interventions.

A strength of our study is the use of integrative mixed methods analysis which has enabled us to explore the relationship between development work and outcome. This rarely used approach in evidence synthesis[11] has given us a unique insight that would not have been possible using a quantitative or qualitative analysis alone. A limitation of our work could be the focus on a single UK funding stream which does not necessarily reflect the body of research funded from other sources and therefore the quality of intervention development work is not necessarily generalizable. However, the fact the NIHR HTA programme is the single largest funder of randomised controlled trials of applied health research in the UK that published detailed monographs of their funded studies, several of which were over 200 pages in length, along with supporting publications provided a detailed and rich source of data beyond what would normally be available in journal-based peer reviewed publications alone. We were able to retain the essence and nuances of the qualitative data whilst developing categorical ratings of quality to help us better explore the relationship between development work and treatment success.

Our findings are similar to those of Dent and Raftery[9] in relation to those trials showing a benefit who reported 19% (16/85) of studies found in favour of the new intervention. It has been suggested that a 50% success rate is a good investment for healthcare research,[17] however, our findings indicate that the studies we reviewed fell well below this. In contrast,, we observed a considerably larger proportion of true negative studies (8/15; 53%) compared with 19/85 (22%) reported by Dent and Raftery.[9] The difference is even greater when compared with a review of cancer trials in the USA where only 2% of trials found a true negative outcome.[10] The reasons for the differences are unclear but could include the pragmatic nature of HTA funded trials and the relative smaller effect sizes often associated with trials of rehabilitation.[18]

It has been recently suggested that RCTs should only be undertaken if they are justified both scientifically and ethically by having a clear hypothesis and established uncertainty[19] and our findings support that by way of good quality intervention development work. Our findings also align with the

elements suggested to be key for developing interventions and reducing research waste by increasing the likelihood of success[20] which will form a comprehensive supplement to the development phase of the MRC Framework. By increasing effort and focus on developing rehabilitation and other interventions in the future researchers and funding bodies could increase the possibility of a definitive trial reporting significant findings after much investment of time and money.

## CONCLUSIONS

Despite much research effort and funding, only four out of fifteen evaluations of 'new' rehabilitation interventions funded by the NIHR HTA programme were found to be unequivocally effective. Most studies reported no difference in outcome between study arms. We have used mixed methods research to explore the relationship between intervention development work and treatment success and developed a method of assessing the quality of this work which suggests comprehensive intervention development work may have a positive relationship with treatment success.

## RECOMMENDATIONS

As this was an exploratory study, further work should be undertaken to establish the validity of quality assessment of intervention development work. This said, researchers and funding agencies should not undervalue the potential benefit of high quality intervention development work prior to definitive randomised controlled trials to reduce the likelihood of a null outcome and improve current rates of treatment success.

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## COMPETING INTERESTS

None

## AUTHOR CONTRIBUTION

VG: Conception and design, data collection, analysis and interpretation, drafting and approving the manuscript;

JH: Design, data collection, analysis and interpretation, drafting and approving the manuscript;

JF: Data collection, analysis, revising and approving the manuscript;

KF: Data collection, revising and approving the manuscript;

CP: Data collection, revising and approving the manuscript;

DR: Conception, revising and approving the manuscript.

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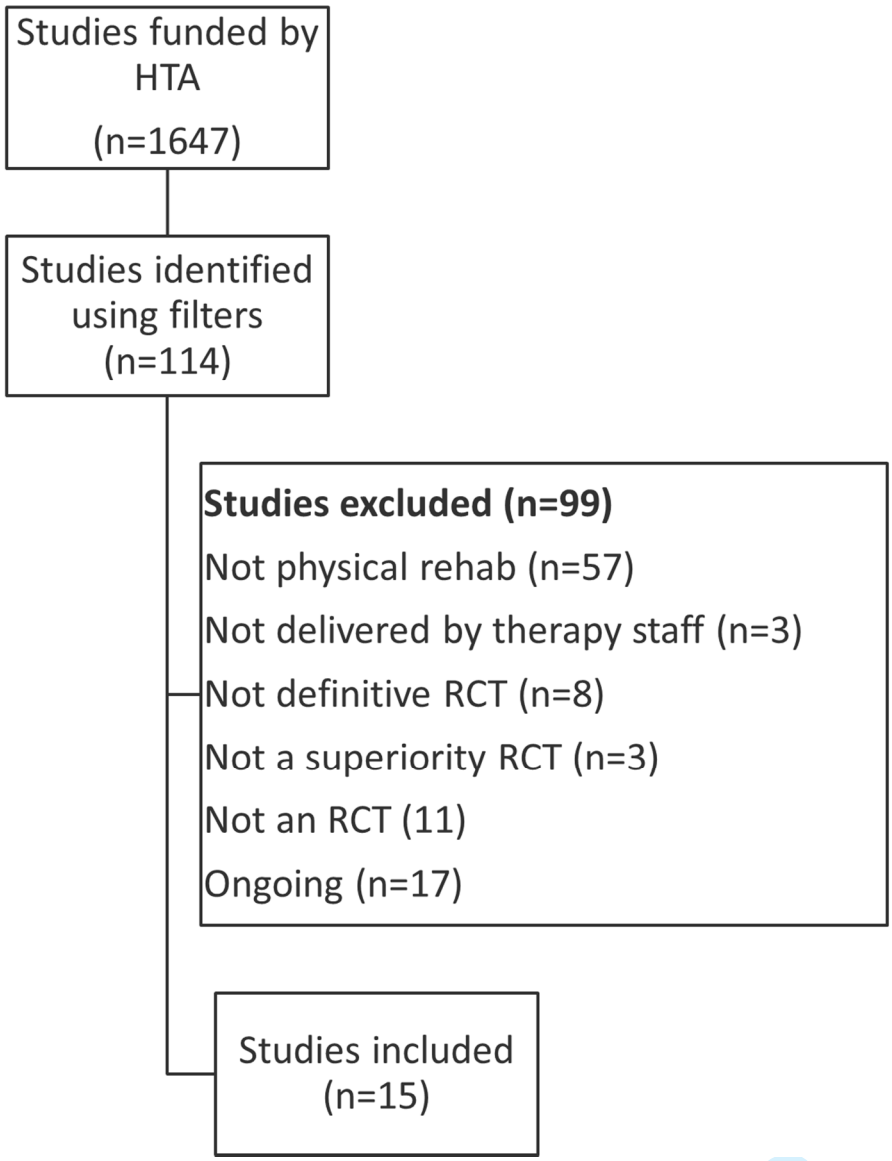


Figure 1 Study selection

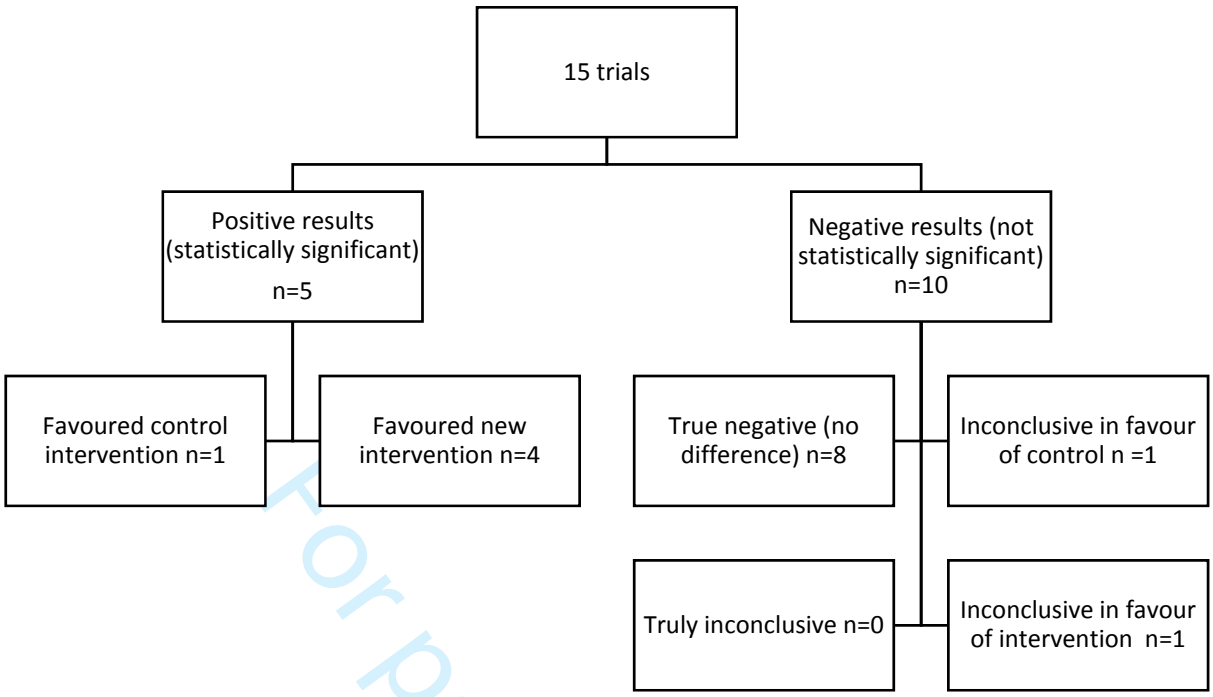


Figure 1 Classification of primary outcome

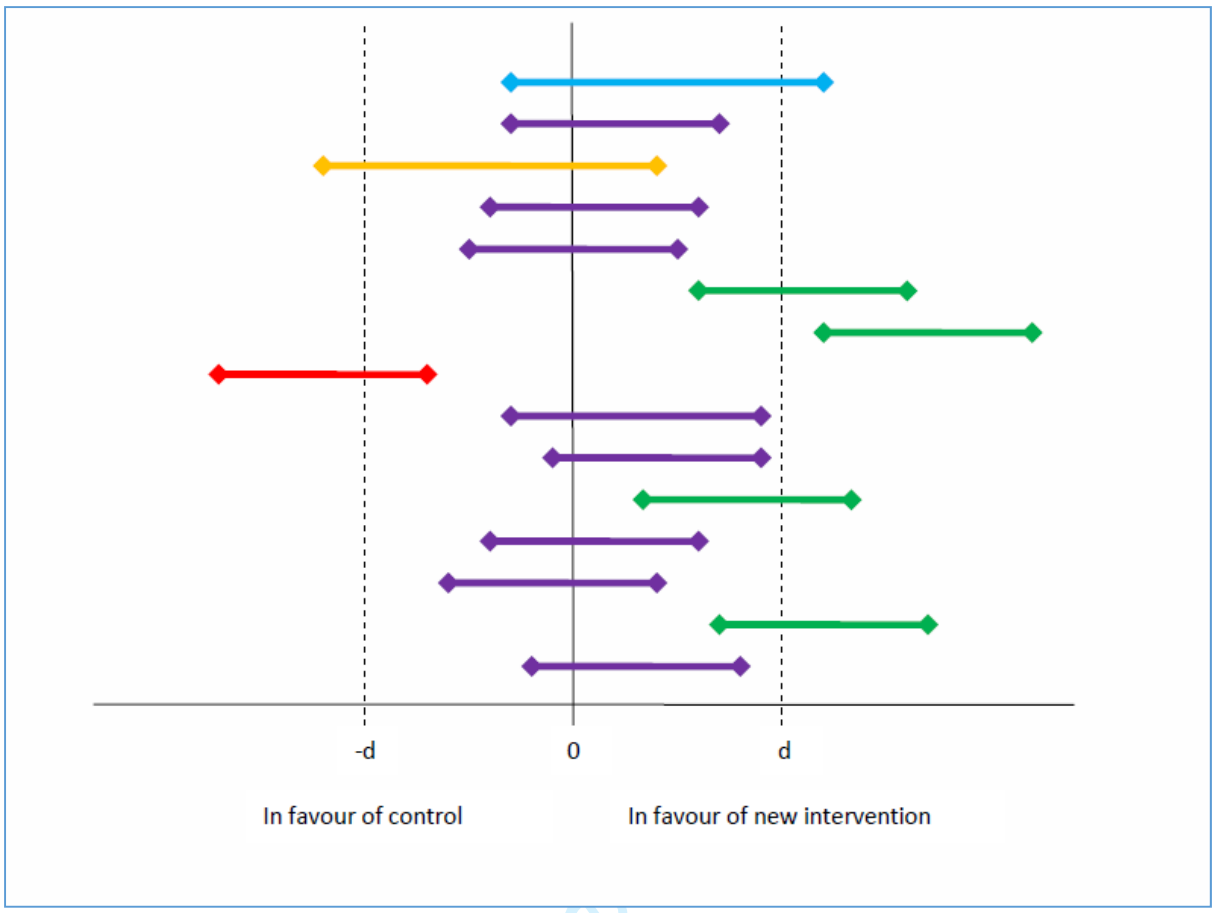


Figure 1 Treatment success of included trials based on 95% Confidence Interval and Minimal Clinically Important Difference from trial sample size calculation (d)

Key: *Green = statistically significantly in favour of intervention; Red = statistically significantly in favour of control; Blue = Inconclusive in favour of intervention; Yellow = Inconclusive in favour of control; Purple = True negative (no difference)*

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# Intervention development and treatment success in UK Health Technology Assessment funded trials of rehabilitation: a mixed methods analysis

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**Keywords**

Rehabilitation, randomised controlled trials, quality, intervention development, mixed methods

## Abstract

**Objectives:** Physical rehabilitation is a complex process and trials of rehabilitation interventions are increasing in number but often report null results. This study aimed to establish treatment success rates in physical rehabilitation trials funded by the National Institute of Health Research Health Technology Assessment (NIHR HTA) programme and examine any relationship between treatment success and the quality of intervention development work undertaken.

**Design:** Mixed methods study

**Setting:** UK

**Methods:**

The NIHR HTA portfolio was searched for all completed definitive randomised controlled trials of physical rehabilitation interventions from inception to July 2016. Treatment success was categorised according to criteria developed by Djulbegovic and colleagues. Detailed textual data regarding any intervention development work were extracted from trial reports and supporting publications and informed the development of quality ratings. Mixed methods integrative analysis was undertaken to explore the relationship between quantitative and qualitative data using joint displays.

**Results:** Fifteen trials were included in the review. Five reported a definitive finding, four of which were in favour of the 'new' intervention. Eight trials reported a true negative (no difference) outcome. Integrative analysis indicated those with lower quality intervention development work were less likely to report treatment success.

**Conclusions:** Despite much effort and funding, most physical rehabilitation trials report equivocal findings. Greater focus on high quality intervention development may reduce the likelihood of a null result in the definitive trial, alongside high quality trial methods and conduct.

**Strengths and limitations of this study:**

- To our knowledge, this study is the first to use mixed methods integrative analyses to explore the relationship between quality of intervention development work and treatment success.
- Using the NIHR HTA Journal monographs, published protocols and other supporting publications for each study together provided a detailed and rich source of data beyond what would be found in a single traditional journal publication.
- The study reviewed randomised controlled trials of physical rehabilitation from a single UK funder as an exemplar and therefore findings may not be representative of other complex interventions or other funding bodies.

## BACKGROUND

Rehabilitation is *"a set of interventions designed to optimise function and reduce disability in individuals with health conditions in interaction with their environment".*[1] and is an essential aspect of healthcare provision. By its very nature rehabilitation in clinical practice is an individually focused, complex activity, involving interventions that are multi-faceted and often implicit in nature[2] and as such, historically, this has been viewed as a barrier to undertaking research.[3] This said, there is a growing body of randomised controlled trials (RCTs) of rehabilitation, suggesting that these challenges can be overcome.[4] This may, in part, be supported by the publication of the Medical Research Council (MRC) Framework for developing and evaluating complex interventions.[5 6]

The MRC framework was developed to optimise the likelihood that new interventions are not rejected as being ineffective when inadequate effort has been made in the development of the intervention.[7] Likewise, Chalmers and Glasziou[8] highlighted the importance of avoiding research waste and recommended that sufficient effort is made to ensure the relevant research questions are identified and addressed using high quality research methods. However, there appears to have been no formal evaluation of the impact of using the development component of the framework on trial outcomes and whether we are observing evidence of effective interventions being developed.

Previous UK[9] and USA[10] reviews synthesised successful and non-successful treatment outcomes from trials of new interventions in order to assess the equipoise principle and to understand what return has been achieved on the investment made by those taking part in the trials, researchers and funders. Dent and Raftery[9] reported 24% (20/85) primary outcome comparisons as having a positive result, of which 16/85 (19%) were in favour of the new intervention, with 19/85 (22%) comparisons reporting a true negative outcome. However, these authors did not focus on rehabilitation interventions, nor did they seek to understand factors that may impact on treatment success, such as the quality or intensity of intervention development pre-trial procedures. Informal discussions with colleagues in the UK and internationally noted that an increasing number of publically funded, large RCTs evaluating physical rehabilitation interventions had reported null findings. Similar concerns have been reported in studies of public health interventions.[11 12] Our study, therefore, sought to assess this observation and also explore whether intervention development activities contributed to treatment success using the National Institute of Health Research Health Technology Assessment programme (NIHR HTA) as an exemplar.

We aimed to use data from the NIHR HTA to:

(a) Establish the treatment outcomes of funded RCTs of physical rehabilitation;

(b) Establish how many new interventions were found to be effective;

(c) Examine what work had been done in terms of developing the new intervention;

(d) Examine the relationship between (a) and (c).

We adopted a mixed methods approach to address the study aims. Although evidence of using integrative mixed methods approaches in synthesising evidence on complex interventions is limited, mixing together qualitative and quantitative data can generate understanding that has the potential to be greater than the sum of the individual parts.[13]

## METHODS

### Design

We undertook a review of NIHR HTA funded randomised controlled trials of physical rehabilitation interventions using narrative synthesis of outcomes and mixed methods analysis of the relationship between intervention development and categorical treatment outcomes using joint displays.

### *Patient and Public Involvement*

Patients and the public were not involved in this study.

### *Data sources and inclusion criteria*

We included superiority randomised controlled trials of physical rehabilitation funded by the NIHR HTA programme. The interventions could be delivered by a single profession or be multi-professional. The NIHR HTA programme is the leading public funding source for randomised controlled trials (RCTs) in the UK and trials of rehabilitation are increasingly part of the portfolio. We only included completed RCTs whose main trial findings were reported in an HTA monograph or peer-reviewed publication in order to establish treatment success. We excluded: pilot and feasibility RCTs as they do not aim to assess the efficacy or effectiveness of interventions;[14] studies where the interventions were primarily psychological or cognitive as the focus of the study was physical rehabilitation; where there was a lack of a clear primary outcome (including primary time point) or where the primary outcome findings were not reported with a 95% confidence interval (CI) as these data were required to assess treatment success.

### *Search and screening*

We searched the HTA Project Portfolio (since superseded by the NIHR Journals Library https://www.journalslibrary.nihr.ac.uk/#/) from inception to July 2016 using the following keywords: physiotherap*OR occupational therap* OR speech and language therap* OR rehabilitation. We removed duplicates and then titles and scientific abstracts were reviewed for potential inclusion by one person and checked by a second. Subsequently full text reports were screened for inclusion by one person and checked by a second. Any disagreements were discussed and agreed with a third person.

### *Data extraction*

All data were extracted by one person and checked by a second. Discrepancies were discussed and resolved with a third person.

*Quantitative Trial data:* Data extracted from each trial publication included trial design, target population, health categories (using the Health Research Classification System), primary outcome(s) and time point, minimal important clinical difference (MCID) that the trial aimed to detect, planned and achieved sample size, and primary outcome results with 95% CI. We also recorded the professional background of the Chief Investigator and amount of funding awarded.

*Qualitative Intervention development data*: Using the revised version of Criteria for Reporting the Development and Evaluation of Complex Interventions (CReDECI 2)[15] and the Template for

Intervention Description and Replication checklist (TIDieR)[16] as frameworks we extracted all available documentary (qualitative) data from the body of the text regarding intervention development, including descriptions of underlying theory, intervention components and reasons for selection, intended interactions between components, contextual considerations, piloting of intervention and impact of definitive intervention to be evaluated, control components, planned intervention delivery and materials. Where additional supporting publications were cited, such as a protocol or intervention development studies, we used these as additional sources of documentary data.

**Data analysis**

We used summary statistics to describe the characteristics of the included studies. We categorised primary outcome findings into one of six treatment outcome categories as described by Djulbegovic and colleagues,[10] these being: 1) statistically significant in favour of the new treatment, 2) statistically significant in favour of the control treatment 3) true negative, 4) truly inconclusive, 5) inconclusive in favour of new treatment or 6) inconclusive in favour of the control treatment. This was achieved by comparing the 95% confidence interval for the difference in primary outcome to the difference specified in the sample size calculation.[9] If the 95% confidence interval excluded a meaningful difference in either direction, implying the treatments have similar effects, the results were categorised as true negative. If the 95% confidence interval included a meaningful difference in either direction (i.e. trial failed to answer the primary question), the results were categorised as being truly inconclusive.

Where a single primary outcome and primary time point were not explicitly identified we utilised the following hierarchy to determine which primary outcome would be used in the analysis:

- Explicitly defined primary outcome
- Outcome used in power calculation
- Main outcome stated in trial objectives
- First outcome reported in sample size calculation

If a primary time point was not reported we used the first follow up time point as this is when we would expect the intervention to have had the greatest effect.

Our preliminary analysis of the qualitative documentary data involved the reading and re-reading of source documents and the extracted descriptions to consolidate our understanding of the development work undertaken in each study. Using a reflective and iterative process we undertook thematic analysis to distil, structure and make sense of intervention development activity by coding and organising data into themes and subthemes. Each theme and sub-theme provided a coherent description of the development work undertaken for each study, which were then synthesised into short descriptors to allow us to produce summary tables. The summary tables comprised a row for each study with columns for each theme and, where relevant, each subtheme. A second researcher checked, discussed and refined descriptors to ensure accuracy. From these descriptions we then developed descriptive ratings on the quality of the intervention development. Depending on the nature of the data, ratings were categorised and the iterative process involved two researchers refining and checking ratings to ensure they reflected the summary data from each study. In order to provide a visual representation of the quality of intervention development work these ratings were then converted to a quality coding to indicate high quality, some or unclear quality or limited quality.

To examine the relationship between intervention development and treatment success, we applied mixed methods analytical techniques in novel ways. For each study, we combined ratings derived from the qualitative data on intervention development with the quantitative data on treatment outcomes in a joint display.

## RESULTS

We included fifteen RCTs (Figure 1),[17-31] of which thirteen used a two-arm, parallel RCT design, one was a two-arm cluster RCT and one was a four-arm factorial design (of which only two arms related to physical rehabilitation). Table 1 provides a summary of the population, intervention, control and outcomes for each study. The combined sample size was 9035 participants, 7834 of whom provided primary outcome data. Five primary outcomes were symptom-based or clinical outcomes, seven were functional measures, two were combined measures and one assessed quality of life. Primary time points varied from immediately post-intervention to one year (median 6 months). The health categories were: Stroke (n=4), Neurological conditions (n=2), Inflammatory/Immune system disorders (n=2), Respiratory (n=1), Musculoskeletal (n=1), Cardiovascular (n=1), Mental Health (n=1), Accident/injuries (n=1), Renal/urogenital (n=1) and other (n=1). Seven interventions were delivered by physiotherapists, one by occupational therapists, one by speech and language therapists, one by nurses, two could be delivered by either a physiotherapist or a nurse, two could be delivered by a physiotherapist or an occupational therapist and one was delivered by both a physiotherapist and an occupational therapist. The Chief Investigators leading the studies were physicians (n=7), physiotherapists (n=5), occupational therapists (n=1), psychologists (n=1) and methodologists (n=1). The total amount of research funding awarded was £11,361,182.

One third of studies (5/15) reported a definitive finding in favour of one of the treatment arms - four studies in favour of the new treatment, one in favour of the control. Of those with negative results, eight studies reported a true negative (no difference) outcome, one was inconclusive in favour of the new treatment, and one inconclusive in favour of the control treatment (Figures 2 and 3).

Qualitative data informed two themes and ten sub-themes which enabled us to develop data-driven quality ratings:

1. *Preparatory work* (Need for the study, underpinning theory for the intervention, co-design, context considerations and intervention piloting)
2. *Intervention and control* (Intervention content and dose, individual tailoring, adherence strategies, standardised training, control content and dose)

Table 2 provides examples of summary data underpinning each rating. Table 3 presents the integrative qualitative and quantitative analysis using a joint display. No single study was deemed to be high quality in each sub-theme. This said, the two best rated studies reported only expert clinical input into co-designing the intervention with a lack of clear patient and public involvement, however, they reported a definitive trial outcome in favour of the new intervention. There does not appear to be a single aspect of intervention development driving study outcomes. This said, those with lower quality development work appear more likely to show no difference in outcomes compared with those with higher quality development work. Some areas of intervention development appear to be improving

with time, these being articulating a clear need and theoretical underpinning, co-design, piloting and descriptions of intervention and control components.

Table 1 Summary of included studies

| Author (year published) | Population (sample size) | Intervention | Control | Primary Outcome |
|---|---|---|---|---|
| McCarthy et al (2004) | People with knee osteoarthritis (n=225) | Twice weekly exercise group for 8 weeks plus home exercises | Home exercises | Aggregate Locomotor Function score |
| Vickers et al (2004) | People with chronic headache (n=401) | Up to 12 acupuncture treatments plus usual care | Usual care from General Practitioner | Weekly headache score |
| Epps et al (2005) | Children with juvenile arthritis (n=101) | 8 hydrotherapy and 8 land based sessions over 2 weeks followed by weekly/fortnightly hydrotherapy for 2 months | 16 land based exercise sessions over 2 weeks followed by weekly or fortnightly land based exercise sessions | Disease activity calculated from Childhood Health Assessment Questionnaire (CHAQ), physicians' global assessment of disease activity, patients' global assessment of overall well-being, number of joints with limited ROM, number of active joints, erythrocyte sedimentation rate. |
| Weindling et al (2007) | Children with cerebral palsy (n=88) | Regular physiotherapy (usual care) plus additional weekly session from physiotherapy assistant for 6 months | Usual care (regular physiotherapy) | Gross Motor Function Measure |
| Jolly et al (2007) | People with myocardial infarction or revascularisation (n=525) | Home-based self-help manual plus up to 3 face to face and 1 phone call support over 12 weeks | Centre-based cardiac rehabilitation | Multiple primary outcomes (Incremental shuttle walk test; Hospital anxiety and depression scale; smoking; blood pressure; serum cholesterol) |
| Lawson et al (2010) | People with Chronic Obstructive Pulmonary Disease (n=326) | Twice weekly community-based pulmonary rehabilitation | Twice weekly hospital-based pulmonary rehabilitation | Endurance Shuttle Walk Test |
| Glazener et al (2011) | Men with incontinence post-prostate surgery (n=853) | Assessment and treatment and exercise over 4 face to face sessions plus advice leaflet | Advice leaflet | Self-reported urinary incontinence |
| Bowen et al (2012) | Adults with aphasia or dysarthria after stroke (n=170) | Speech and language therapy visits up to 3 sessions per week for up to 16 weeks | Volunteer visits up to 3 sessions per week for up to 16 weeks | Therapy Outcome measure |
| Lamb et al (2012) | People with whiplash with persistent symptoms (n=599) | 6 sessions of assessment and treatment/exercise over 8 weeks | Single session of advice | Neck Disability Index |
| Underwood et al (2013) | Care home residents (n=781) | Twice weekly exercise group for a year | Depression awareness training for care home staff | Geriatric Depression Scale |
| Logan et al (2014) | People with stroke (n=568) | Up to 12 therapy visits to increase outdoor mobility plus verbal/written advice | Verbal/written advice | SF-36 Social Function domain |
| Williams et al (2015) | People with rheumatoid arthritis (n=490) | 6 sessions of exercise plus home exercises over 12 weeks | Single assessment advice session with 2 further optional sessions over 12 weeks (no exercises) | Michigan Hand Outcome Questionnaire |
| Langhorne et al (2015) | People with stroke (n=2104) | 3 additional out of bed sessions per day for up to 2 weeks | Usual care | Modified Rankin Scale |
| Sackley et al (2016) | Care home residents with stroke (n=1042) | Individualised occupational therapy | No occupational therapy | Barthel Index |
| Clarke et al (2016) | People with Parkinson's (n=762) | Up to 8 individualised sessions of Physiotherapy and up to 8 individualised sessions of occupational therapy | No therapy | Nottingham Extended Activities of Daily Living |

Table 2 Description of themes, subthemes and quality ratings with examples

| Theme | Sub-theme | Description of rating | Examples of data supporting rating | Rating |
|---|---|---|---|---|
| **Preparatory work** | **Need for the study** | Multiple sources of evidence of need for the study e.g. recent systematic review, guidelines, high level reports, commissioned research, national audit | International task force highlighted lack of evidence and need for evaluation. Cochrane review drew similar conclusions. | ▲ |
| | | Single source of evidence / non-systematic review to support need for study | Old systematic review indicates paucity of high quality research. | ■ |
| | | Lack of clarity or underpinning evidence regarding need for study | Poor justification for this study. Evidence cited doesn't support the need for this particular study. | ● |
| | **Theoretical underpinning** | Theoretical underpinning described | Physiological and psychological theories underpinning the intervention described in detail. | ▲ |
| | | Lacks clear theoretical underpinning | No information provided regarding the theoretical basis for the intervention provided. | ■ |
| | **Co-design** | Good PPI and expert clinical input | Patients and clinicians helped develop the intervention. | ▲ |
| | | Good PPI but weak or no expert clinical input / Good clinical input but unclear or no PPI | Clinicians contributed to the intervention development but no indication of service user involvement. | ■ |
| | | No co-design | No co-design was undertaken to develop the intervention. | ● |
| | **Contextual considerations** | Context considered | The use of different professionals in delivering the intervention reflected the real world situation of how this would occur in practice. | ▲ |
| | | Context not adequately considered | There was a lack of understanding of relevant context and factors needed for intervention development and delivery. | ● |
| | **Piloting of intervention** | Pilot conducted, evaluated and findings addressed for main evaluation | The pilot data helped refine the intervention for evaluation in the main trial. | ▲ |
| | | Pilot conducted but findings not clearly addressed in intervention for main evaluation | The pilot work led to a modification of the control intervention but unclear as to whether this also happened for the novel intervention. | ■ |
| | | No pilot reported | No piloting of intervention reported | ● |

| | | | | |
|---|---|---|---|---|
| **Intervention and control** | **Content and dose** | Intervention components and dose clearly described | The content and the dose of the exercise programme was described in detail. | ▲ |
| | | Intervention components clearly described but dose was not standardised | The content of the programme was well described but no specific dose was prescribed. | ■ |
| | | Intervention not replicable from description of components and dose | Intervention was based on usual practice and had no protocol or guidance on minimum dose. | ● |
| | **Tailoring** | Formalised assessment to inform tailoring | An assessment tool was used to determine the individuals level of exercise intensity | ▲ |
| | | Clinical judgement only used to inform tailoring | Therapists used their clinical judgement to individually tailor programmes. | ■ |
| | | Not adequately reported | Intervention individually tailored but no information as to how this was undertaken. | ● |
| | **Adherence support strategies** | Explicit strategies to support adherence to the intervention clearly reported | Specific adherence strategies described as part of the intervention. | ▲ |
| | | No clear information regarding adherence support strategies | No information reported regarding adherence strategies. | ● |
| | | Supporting adherence is not relevant to the intervention | The intervention was passive and adherence strategies not relevant. | NA |
| | **Intervention training** | Standardised training in intervention received +/- additional/ongoing support or training | Staff attended a 1.5 day training session and had an additional support session with ongoing contact from research team. | ▲ |
| | | No standardised intervention training received but staff delivering described to be experienced in the intervention or training of staff unclear/not reported | Staff have post graduate training in the intervention but no study specific training reported. | ■ |
| | **Control description** | Active control/attention control/usual care with some standardised components | Control was an active intervention that differed from intervention only in terms of delivery setting. | ▲ |
| | | Usual care had no standardised components | Control was usual care and was not standardised between sites. | ■ |

Key: ▲ High quality ■ Some/Unclear quality ● Limited quality

Table 3 Joint display of the quality of intervention development work of NIHR funded trial of rehabilitation and treatment success

| Author | Need | Theory | Co-design | Context | Pilot | Intervention Content | Tailored | Adherence strategies | Training delivery | Control description | Treatment success |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Lamb[23] | ▲ | ▲ | ■ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | Statistically significant in favour of intervention |
| Williams[31] | ▲ | ▲ | ■ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | Statistically significant in favour of intervention |
| Underwood[32] | ▲ | ▲ | ■ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | True negative (No difference) |
| Glazener[20] | ▲ | ▲ | ▲ | ▲ | ● | ▲ | ▲ | ▲ | ▲ | ▲ | True negative (No difference) |
| Logan[24] | ▲ | ▲ | ▲ | ▲ | ■ | ■ | ▲ | ▲ | ▲ | ▲ | True negative (No difference) |
| Bowen[17] | ▲ | ▲ | ■ | ▲ | ▲ | ■ | ▲ | ▲ | ■ | ▲ | Inconclusive in favour of intervention |
| AVERT Group[21] | ▲ | ▲ | ● | ▲ | ■ | ▲ | ▲ | NA | ▲ | ■ | Statistically significant in favour of control |
| Sackley[26] | ▲ | ▲ | ■ | ▲ | ■ | ● | ▲ | ▲ | ■ | ■ | True negative (No difference) |
| Jolly[22] | ● | ▲ | ● | ▲ | ● | ▲ | ■ | ▲ | ▲ | ■ | True negative (No difference) |
| McCarthy[25] | ■ | ■ | ● | ▲ | ● | ▲ | ▲ | ■ | ■ | ▲ | Statistically significant in favour of intervention |
| Waterhouse[29] | ▲ | ■ | ● | ● | ● | ▲ | ■ | ▲ | ■ | ▲ | True negative (No difference) |
| Epps[19] | ■ | ▲ | ■ | ● | ■ | ▲ | ■ | ■ | ■ | ▲ | Inconclusive in favour of control |
| Clarke[18] | ● | ■ | ■ | ▲ | ● | ● | ▲ | ■ | ■ | ■ | True negative (No difference) |
| Vickers[28] | ■ | ■ | ● | ▲ | ● | ● | ● | NA | ■ | ■ | Statistically significant in favour of intervention |
| Weindling[30] | ● | ▲ | ● | ● | ● | ● | ● | ■ | ■ | ■ | True negative (No difference) |

Key:

▲ High quality ■ Some/Unclear quality ● Limited quality

## DISCUSSION

We found that only one third (5/15) of the randomised controlled trials of rehabilitation funded by the NIHR HTA programme successfully demonstrated a statistically significant effect for one of the randomised groups in each trial. Four (27%) trials found an effect in favour of the 'new' intervention. Although we would not expect all studies to demonstrate effectiveness in favour of the 'new' intervention, the equipoise principle implies that there would be no difference between the proportion of studies favouring intervention or control[9]. However, this doesn't account for a null outcome. We were able to use contemporary research methods to develop an assessment of the quality of development work and assessed the included trials to be of varied quality in terms of intervention development work. In general, we found that those studies with poorer quality intervention development work were less likely to report treatment success and were more likely to lead to results categorised as truly negative, i.e. which excluded a meaningful difference in outcome in either direction. Two studies[23 31] with high quality intervention development reported treatment success although two older[25 28] and possibly less well reported trials also reported effective interventions. Developments in complex intervention evaluation[5], reporting standards[16 33] and involving patients and the public in research[34] have occurred since the inception of the HTA programme and as such some development work may have been undertaken but not reported in the older studies. A recent overview of approaches to developing interventions noted the absence of patient and public involvement[35]. In addition, there was limited evidence of piloting the intervention prior to proceeding to the full trial with only four studies reporting this having been done. Most (> 80%) drug intervention development studies fail to reach the 'Phase III' trial stage.[36] Public health interventions have tended to go straight to an RCT without piloting which may contribute to challenges in demonstrating effectiveness.[11] There are of course other factors that influence trial findings, including trial methods and conduct, however our question was specifically determined to explore what, if any, relationship existed between intervention development and outcomes and not in the effectiveness of particular interventions.

A strength of our study is the use of integrative mixed methods analysis which has enabled us to explore the relationship between development work and outcome. This rarely used approach in evidence synthesis[37] has given us a unique insight that would not have been possible using a quantitative or qualitative analysis alone. A limitation of our work could be the focus on a single UK funding stream which does not necessarily reflect the body of research funded from other sources and therefore the quality of intervention development work is not necessarily generalizable. However, the NIHR HTA programme is the single largest funder of randomised controlled trials of applied health research in the UK. They publish detailed monographs of their funded studies, along with protocols and other supporting publications that provide a detailed and rich source of data beyond what would normally be available in journal-based peer reviewed publications alone. We were able to retain the essence and nuances of the qualitative data whilst developing categorical ratings of quality to help us better explore the relationship between development work and treatment success.

Our findings are similar to those of Dent and Raftery[9] in relation to those trials showing a benefit who reported 19% (16/85) of studies found in favour of the new intervention. It has been suggested that a 50% success rate is a good investment for healthcare research,[38] however, our findings indicate that the studies we reviewed fell well below this. In contrast, we observed a considerably larger proportion of true negative studies (8/15; 53%) compared with 19/85 (22%) reported by Dent and Raftery.[9] The

difference is even greater when compared with a review of cancer trials in the USA where only 2% of trials found a true negative outcome.[10] The reasons for the differences are unclear but could include the pragmatic nature of HTA funded trials and the relative smaller effect sizes often associated with trials of rehabilitation.[39]

It has been recently suggested that RCTs should only be undertaken if they are justified both scientifically and ethically by having a clear hypothesis and established uncertainty[40] and our findings support that by way of good quality intervention development work. Our findings also align with the elements suggested to be key for developing interventions and reducing research waste by increasing the likelihood of success[41] which will form a comprehensive supplement to the development phase of the updated MRC guidance on developing and evaluating interventions due for publication in 2019. The NIHR HTA is publically funded and by increasing effort and focus on developing rehabilitation and other interventions in the future researchers and funding bodies could increase the possibility of a definitive trial reporting beneficial findings after much investment of time and public money.

## CONCLUSIONS

Despite much research effort and funding, only four out of fifteen evaluations of 'new' rehabilitation interventions funded by the NIHR HTA programme were found to be unequivocally effective. Most studies reported no difference in outcome between study arms. We have used mixed methods research to explore the relationship between intervention development work and treatment success and developed a method of assessing the quality of this work which suggests comprehensive intervention development work may have a positive relationship with treatment success.

## RECOMMENDATIONS

As this was an exploratory study, further work should be undertaken to establish the validity of quality assessment of intervention development work. This said, researchers and funding agencies should not undervalue the potential benefit of high quality intervention development work prior to definitive randomised controlled trials to reduce the likelihood of a null outcome and improve current rates of treatment success.

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## COMPETING INTERESTS

None

## DATA SHARING STATEMENT

No additional data are available.

## AUTHOR CONTRIBUTION

VG: Conception and design, data collection, analysis and interpretation, drafting and approving the manuscript;

JH: Design, data collection, analysis and interpretation, drafting and approving the manuscript;

JF: Data collection, analysis, revising and approving the manuscript;

KF: Data collection, revising and approving the manuscript;

CP: Data collection, revising and approving the manuscript;

DR: Conception, revising and approving the manuscript.

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**Figure Legends:**

Figure 1 Study selection

Figure 2 Classification of Primary Outcome

Figure 3 Treatment success of included trials based on 95% Confidence Intervals and Minimum Clinically Important Difference from sample size calculation (d)

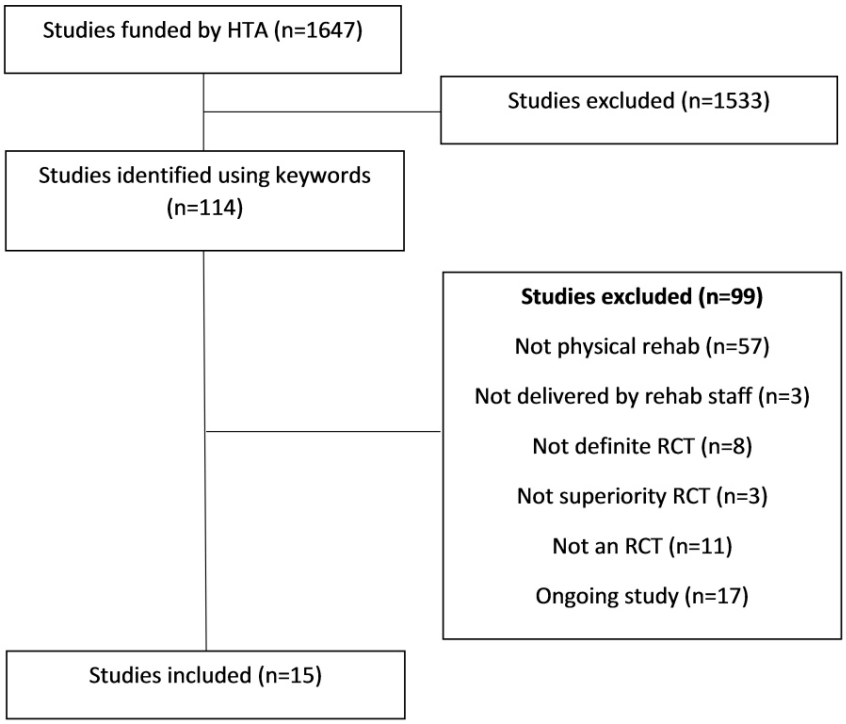


Figure 1 Study selection

Figure 1 Study selection

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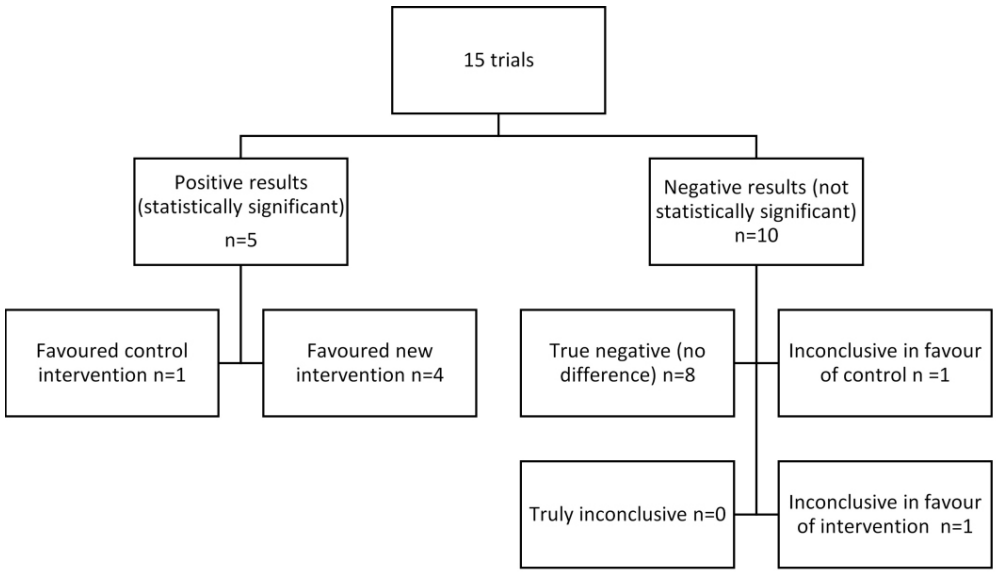


Figure 2 Classification of primary outcome

Figure 2 Classification of Primary Outcome

89x66mm (300 x 300 DPI)

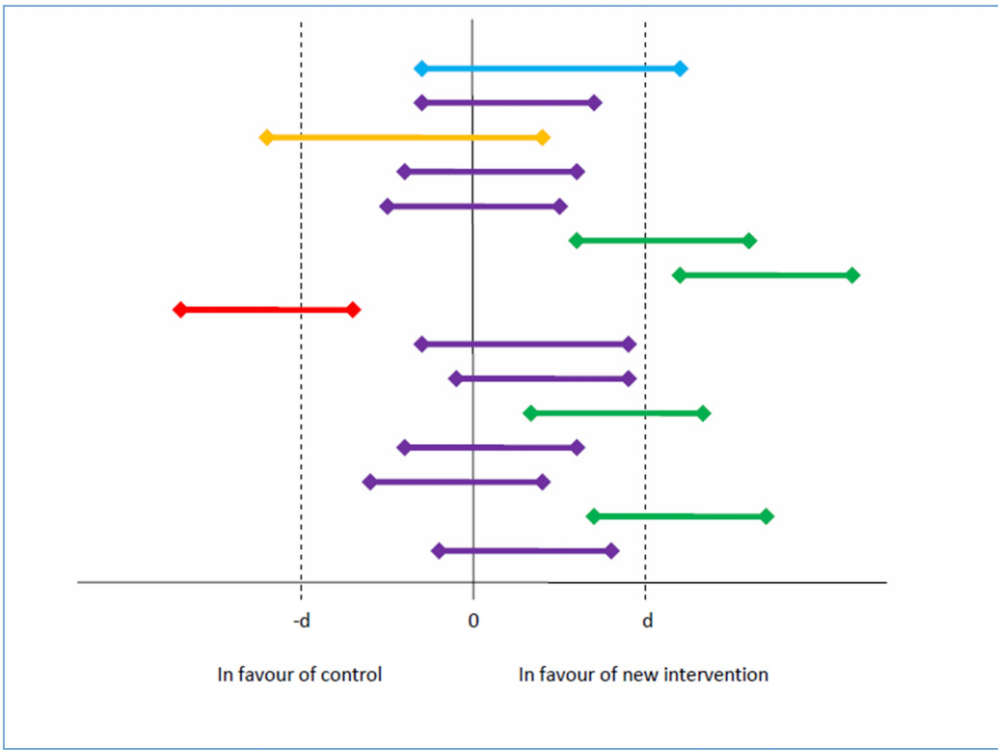


Figure 3 Treatment success of included trials based on 95% Confidence Interval and Minimal Clinically Important Difference from trial sample size calculation (d)

Key: *Green = statistically significantly in favour of intervention; Red = statistically significantly in favour of control; Blue = Inconclusive in favour of intervention; Yellow = Inconclusive in favour of control; Purple = True negative (no difference)*

Figure 3 Treatment success of included trials based on 95% Confidence Intervals and Minimum Clinically Important Difference from sample size calculation (d)

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BMJ Open

# Intervention development and treatment success in UK Health Technology Assessment funded trials of physical rehabilitation: a mixed methods analysis



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# Intervention development and treatment success in UK Health Technology Assessment funded trials of physical rehabilitation: a mixed methods analysis

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**Keywords**

Rehabilitation, randomised controlled trials, quality, intervention development, mixed methods

## Abstract

**Objectives:** Physical rehabilitation is a complex process and trials of rehabilitation interventions are increasing in number but often report null results. This study aimed to establish treatment success rates in physical rehabilitation trials funded by the National Institute of Health Research Health Technology Assessment (NIHR HTA) programme and examine any relationship between treatment success and the quality of intervention development work undertaken.

**Design:** Mixed methods study

**Setting:** UK

**Methods:**

The NIHR HTA portfolio was searched for all completed definitive randomised controlled trials of physical rehabilitation interventions from inception to July 2016. Treatment success was categorised according to criteria developed by Djulbegovic and colleagues. Detailed textual data regarding any intervention development work were extracted from trial reports and supporting publications and informed the development of quality ratings. Mixed methods integrative analysis was undertaken to explore the relationship between quantitative and qualitative data using joint displays.

**Results:** Fifteen trials were included in the review. Five reported a definitive finding, four of which were in favour of the 'new' intervention. Eight trials reported a true negative (no difference) outcome. Integrative analysis indicated those with lower quality intervention development work were less likely to report treatment success.

**Conclusions:** Despite much effort and funding, most physical rehabilitation trials report equivocal findings. Greater focus on high quality intervention development may reduce the likelihood of a null result in the definitive trial, alongside high quality trial methods and conduct.

**Strengths and limitations of this study:**

- To our knowledge, this study is the first to use mixed methods integrative analyses to explore the relationship between quality of intervention development work and treatment success.
- Using the NIHR HTA Journal monographs, published protocols and other supporting publications for each study together provided a detailed and rich source of data beyond what would be found in a single traditional journal publication.
- The study reviewed randomised controlled trials of physical rehabilitation from a single UK funder as an exemplar and therefore findings may not be representative of other complex interventions or other funding bodies.

## BACKGROUND

Rehabilitation is *"a set of interventions designed to optimise function and reduce disability in individuals with health conditions in interaction with their environment".*[1] and is an essential aspect of healthcare provision. By its very nature rehabilitation in clinical practice is an individually focused, complex activity, involving interventions that are multi-faceted and often implicit in nature[2] and as such, historically, this has been viewed as a barrier to undertaking research.[3] This said, there is a growing body of randomised controlled trials (RCTs) of rehabilitation, suggesting that these challenges can be overcome.[4] This may, in part, be supported by the publication of the Medical Research Council (MRC) Framework for developing and evaluating complex interventions.[5 6]

The MRC framework was developed to optimise the likelihood that new interventions are not rejected as being ineffective when inadequate effort has been made in the development of the intervention.[7] Likewise, Chalmers and Glasziou[8] highlighted the importance of avoiding research waste and recommended that sufficient effort is made to ensure the relevant research questions are identified and addressed using high quality research methods. However, there appears to have been no formal evaluation of the impact of using the development component of the framework on trial outcomes and whether we are observing evidence of effective interventions being developed.

Previous UK[9] and USA[10] reviews synthesised successful and non-successful treatment outcomes from trials of new interventions in order to assess the equipoise principle and to understand what return has been achieved on the investment made by those taking part in the trials, researchers and funders. Dent and Raftery[9] reported 24% (20/85) primary outcome comparisons as having a positive result, of which 16/85 (19%) were in favour of the new intervention, with 19/85 (22%) comparisons reporting a true negative outcome. However, these authors did not focus on rehabilitation interventions, nor did they seek to understand factors that may impact on treatment success, such as the quality or intensity of intervention development pre-trial procedures. Informal discussions with colleagues in the UK and internationally noted that an increasing number of publically funded, large RCTs evaluating physical rehabilitation interventions had reported null findings. Similar concerns have been reported in studies of public health interventions.[11 12] Our study, therefore, sought to assess this observation and also explore whether intervention development activities contributed to treatment success using the National Institute of Health Research Health Technology Assessment programme (NIHR HTA) as an exemplar.

We aimed to use data from the NIHR HTA to:

(a) Establish the treatment outcomes of funded RCTs of physical rehabilitation;

(b) Establish how many new interventions were found to be effective;

(c) Examine what work had been done in terms of developing the new intervention;

(d) Examine the relationship between (a) and (c).

We adopted a mixed methods approach to address the study aims. Although evidence of using integrative mixed methods approaches in synthesising evidence on complex interventions is limited, mixing together qualitative and quantitative data can generate understanding that has the potential to be greater than the sum of the individual parts.[13]

## METHODS

### Design

We undertook a review of NIHR HTA funded randomised controlled trials of physical rehabilitation interventions using narrative synthesis of outcomes and mixed methods analysis of the relationship between intervention development and categorical treatment outcomes using joint displays.

### *Patient and Public Involvement*

Patients and the public were not involved in this study.

### *Data sources and inclusion criteria*

We included superiority randomised controlled trials of physical rehabilitation funded by the NIHR HTA programme. The interventions could be delivered by a single profession or be multi-professional. The NIHR HTA programme is the leading public funding source for randomised controlled trials (RCTs) in the UK and trials of rehabilitation are increasingly part of the portfolio. We only included completed RCTs whose main trial findings were reported in an HTA monograph or peer-reviewed publication in order to establish treatment success. We excluded: pilot and feasibility RCTs as they do not aim to assess the efficacy or effectiveness of interventions;[14] studies where the interventions were primarily psychological or cognitive as the focus of the study was physical rehabilitation; where the primary outcome findings were not reported with a 95% confidence interval (CI) as these data were required to assess treatment success.

### *Search and screening*

We searched the HTA Project Portfolio (since superseded by the NIHR Journals Library https://www.journalslibrary.nihr.ac.uk/#/) from inception to July 2016 using the following keywords: physiotherap*OR occupational therap* OR speech and language therap* OR rehabilitation. We removed duplicates and then titles and scientific abstracts were reviewed for potential inclusion by one person and checked by a second. Subsequently full text reports were screened for inclusion by one person and checked by a second. Any disagreements were discussed and agreed with a third person.

### *Data extraction*

All data were extracted by one person and checked by a second. Discrepancies were discussed and resolved with a third person.

*Quantitative Trial data:* Data extracted from each trial publication included trial design, target population, health categories (using the Health Research Classification System), primary outcome(s) and time point, minimal important clinical difference (MCID) or percentage change that the trial aimed to detect, planned and achieved sample size, and primary outcome results with 95% CI. We also recorded the professional background of the Chief Investigator and amount of funding awarded.

*Qualitative Intervention development data*: Using the revised version of Criteria for Reporting the Development and Evaluation of Complex Interventions (CReDECI 2)[15] and the Template for Intervention Description and Replication checklist (TIDieR)[16] as frameworks we extracted all available

documentary (qualitative) data from the body of the text regarding intervention development, including descriptions of underlying theory, intervention components and reasons for selection, intended interactions between components, contextual considerations, piloting of intervention and impact of definitive intervention to be evaluated, control components, planned intervention delivery and materials. Where additional supporting publications were cited, such as a protocol or intervention development studies, we used these as additional sources of documentary data.

**Data analysis**

We used summary statistics to describe the characteristics of the included studies. We categorised primary outcome findings into one of six treatment outcome categories as described by Djulbegovic and colleagues,[10] these being: 1) statistically significant in favour of the new treatment, 2) statistically significant in favour of the control treatment 3) true negative, 4) truly inconclusive, 5) inconclusive in favour of new treatment or 6) inconclusive in favour of the control treatment. This was achieved by comparing the 95% confidence interval for the difference in primary outcome to the difference specified in the sample size calculation.[9] If the 95% confidence interval excluded a meaningful difference in either direction, implying the treatments have similar effects, the results were categorised as true negative. If the 95% confidence interval included a meaningful difference in either direction (i.e. trial failed to answer the primary question), the results were categorised as being truly inconclusive.

Where a single primary outcome and primary time point were not explicitly identified we utilised the following hierarchy to determine which primary outcome would be used in the analysis:

- Explicitly defined primary outcome
- Outcome used in power calculation
- Main outcome stated in trial objectives
- First outcome reported in sample size calculation

If a primary time point was not reported we used the first follow up time point as this is when we would expect the intervention to have had the greatest effect.

Our preliminary analysis of the qualitative documentary data involved the reading and re-reading of source documents and the extracted descriptions to consolidate our understanding of the development work undertaken in each study. Using a reflective and iterative process we undertook thematic analysis to distil, structure and make sense of intervention development activity by coding and organising data into themes and subthemes. Each theme and sub-theme provided a coherent description of the development work undertaken for each study, which were then synthesised into short descriptors to allow us to produce summary tables. The summary tables comprised a row for each study with columns for each theme and, where relevant, each subtheme. A second researcher checked, discussed and refined descriptors to ensure accuracy. From these descriptions we then developed descriptive ratings on the quality of the intervention development. Depending on the nature of the data, ratings were categorised and the iterative process involved two researchers refining and checking ratings to ensure they reflected the summary data from each study. In order to provide a visual representation of the quality of intervention development work these ratings were then converted to a quality coding to indicate high quality, some or unclear quality or limited quality. For example under co-design the highest quality rating was given when the intervention was co-

designed with *both* clinical and service user input, a middle rating when *either* clinicians or service users were involved, and the lowest quality rating when *neither* clinicians nor service users were involved.

To examine the relationship between intervention development and treatment success, we applied mixed methods analytical techniques in novel ways. For each study, we combined ratings derived from the qualitative data on intervention development with the quantitative data on treatment outcomes in a joint display.

## RESULTS

We included fifteen RCTs (Figure 1),[17-31] of which thirteen used a two-arm, parallel RCT design, one was a two-arm cluster RCT and one was a four-arm factorial design (of which only two arms related to physical rehabilitation). Table 1 provides a summary of the population, intervention, control and outcomes for each study. The combined target sample size was 7548 participants, 7834 of whom provided primary outcome data, although three studies[19 29 30] were considerably below their target sample size at the primary time point. Five primary outcomes were symptom-based or clinical outcomes, seven were functional measures, two were combined measures and one assessed quality of life. Primary time points varied from immediately post-intervention to one year (median 6 months). The health categories were: Stroke (n=4), Neurological conditions (n=2), Inflammatory/Immune system disorders (n=2), Respiratory (n=1), Musculoskeletal (n=1), Cardiovascular (n=1), Mental Health (n=1), Accident/injuries (n=1), Renal/urogenital (n=1) and other (n=1). Seven interventions were delivered by physiotherapists, one by occupational therapists, one by speech and language therapists, one by nurses, two could be delivered by either a physiotherapist or a nurse, two could be delivered by a physiotherapist or an occupational therapist and one was delivered by both a physiotherapist and an occupational therapist. The Chief Investigators leading the studies were physicians (n=7), physiotherapists (n=5), occupational therapists (n=1), psychologists (n=1) and methodologists (n=1). The total amount of research funding awarded was £12,515,823.

One third of studies (5/15) reported a definitive finding in favour of one of the treatment arms - four studies in favour of the new treatment, one in favour of the control. Of those with negative results, eight studies reported a true negative (no difference) outcome, one was inconclusive in favour of the new treatment, and one inconclusive in favour of the control treatment (Figures 2 and 3).

Qualitative data informed two themes and ten sub-themes which enabled us to develop data-driven quality ratings:

1. *Preparatory work* (Need for the study, underpinning theory for the intervention, co-design, context considerations and intervention piloting)
2. *Intervention and control* (Intervention content and dose, individual tailoring, adherence strategies, standardised training, control content and dose)

Table 2 provides examples of summary data underpinning each rating with Table 3 describing the quality rating for each study in chronological order. Table 4 presents the integrative qualitative and quantitative analysis using a joint display. No single study was deemed to be high quality in each sub-theme. This said, the two best rated studies reported only expert clinical input into co-designing the

intervention with a lack of clear patient and public involvement, however, they reported a definitive trial outcome in favour of the new intervention. There does not appear to be a single aspect of intervention development driving study outcomes. This said, those with lower quality development work appear more likely to show no difference in outcomes compared with those with higher quality development work. Some areas of intervention development appear to be improving with time, these being articulating a clear need and theoretical underpinning, co-design, piloting and descriptions of intervention and control components.

Table 1 Summary of included studies

| Author (year published) | Funding awarded (£) | Population (target sample size/number of participants with primary outcome data) | Intervention | Control | Primary Outcome (MCID or % change study aimed to detect) |
|---|---|---|---|---|---|
| McCarthy et al (2004) | 218,517 | People with knee osteoarthritis (n=152/200) | Twice weekly exercise group for 8 weeks plus home exercises | Home exercises | Aggregate Locomotor Function score (4 seconds) |
| Vickers et al (2004) | 161,532 | People with chronic headache (n=288/301) | Up to 12 acupuncture treatments plus usual care | Usual care from General Practitioner | Weekly headache score (35% reduction) |
| Epps et al (2005) | 152,011 | Children with juvenile arthritis (n=200/74) | 8 hydrotherapy and 8 land based sessions over 2 weeks followed by weekly/fortnightly hydrotherapy for 2 months | 16 land based exercise sessions over 2 weeks followed by weekly or fortnightly land based exercise sessions | Disease status calculated from Childhood Health Assessment Questionnaire (CHAQ), physicians' global assessment of disease activity, parents' global assessment of overall well-being, number of joints with limited ROM, number of active joints, erythrocyte sedimentation rate (30% improvement on 3 measures with < 30% deterioration on remaining 3 measures) |
| Weindling et al (2007) | 334,093 | Children with cerebral palsy (n=153/76) | Regular physiotherapy (usual care) plus additional weekly session from physiotherapy assistant for 6 months | Usual care (regular physiotherapy) | Gross Motor Function Measure (14 points) |
| Jolly et al (2007) | 480,612 | People with myocardial infarction or revascularisation (n=450/487) | Home-based self-help manual plus up to 3 face to face and 1 phone call support over 12 weeks | Centre-based cardiac rehabilitation | Incremental shuttle walk test (6 shuttles); Hospital anxiety and depression scale (1.5 points); smoking cessation (20%); blood pressure (6mmHg systolic); serum cholesterol (0.4 mmol/l) |
| Waterhouse et al (2010) | 460,543 | People with Chronic Obstructive Pulmonary Disease (n=372/162) | Twice weekly community-based pulmonary rehabilitation | Twice weekly hospital-based pulmonary rehabilitation | Endurance Shuttle Walk Test (60% increase in distance walked) |
| Glazener et al (2011) | 1,051,699 | Men with incontinence post-prostate surgery (696/788) | Assessment and treatment and exercise over 4 face to face sessions plus advice leaflet | Advice leaflet | Self-reported urinary incontinence (15% reduction in % of people with urinary incontinence) |
| Bowen et al (2012) | 1,457,533 | Adults with aphasia or dysarthria after stroke (n=170/153) | Speech and language therapy visits up to 3 sessions per week for up to 16 weeks | Volunteer visits up to 3 sessions per week for up to 16 weeks | Therapy Outcome measure (0.5) |
| Lamb et al (2012) | 755,310 | People with whiplash with persistent symptoms (n=422/507) | 6 sessions of assessment and treatment/exercise over 8 weeks | Single session of advice | Neck Disability Index (3 points) |
| Underwood et al (2013) | 1,957,884 | Care home residents (n=409/493) | Twice weekly exercise group for a year | Depression awareness training for care home staff | Geriatric Depression Scale (17.3% reduction in % of people with depression) |
| Logan et al (2014) | 993,080 | People with stroke (n=440/503) | Up to 12 therapy visits to increase outdoor mobility plus verbal/written advice | Verbal/written advice | SF-36 Social function domain (12.5 points) |
| Williams et al (2015) | 976,955 | People with rheumatoid arthritis (n=352/438) | 6 sessions of exercise plus home exercises over 12 weeks | Single assessment advice session with 2 further optional sessions over 12 weeks (no exercises) | Michigan Hand Outcome Questionnaire (0.3) |
| AVERT Group (2015) | 282,372 | People with stroke (n=2104/2083) | 3 additional out of bed sessions per day for up to 2 weeks | Usual care | Modified Rankin Scale-(mRS) (7.1% Absolute risk reduction of a mRS score of 3-6) |

| | | | | | |
|---|---|---|---|---|---|
| Sackley et al (2016) | 1,797,676 | Care home residents with stroke (n=660/870) | Individualised occupational therapy | No occupational therapy | Barthel Index (2 points) |
| Clarke et al (2016) | 1,436,006 | People with Parkinson's (n=680/699) | Up to 8 individualised sessions of Physiotherapy and up to 8 individualised sessions of occupational therapy | No therapy | Nottingham Extended Activities of Daily Living (2.5 points) |

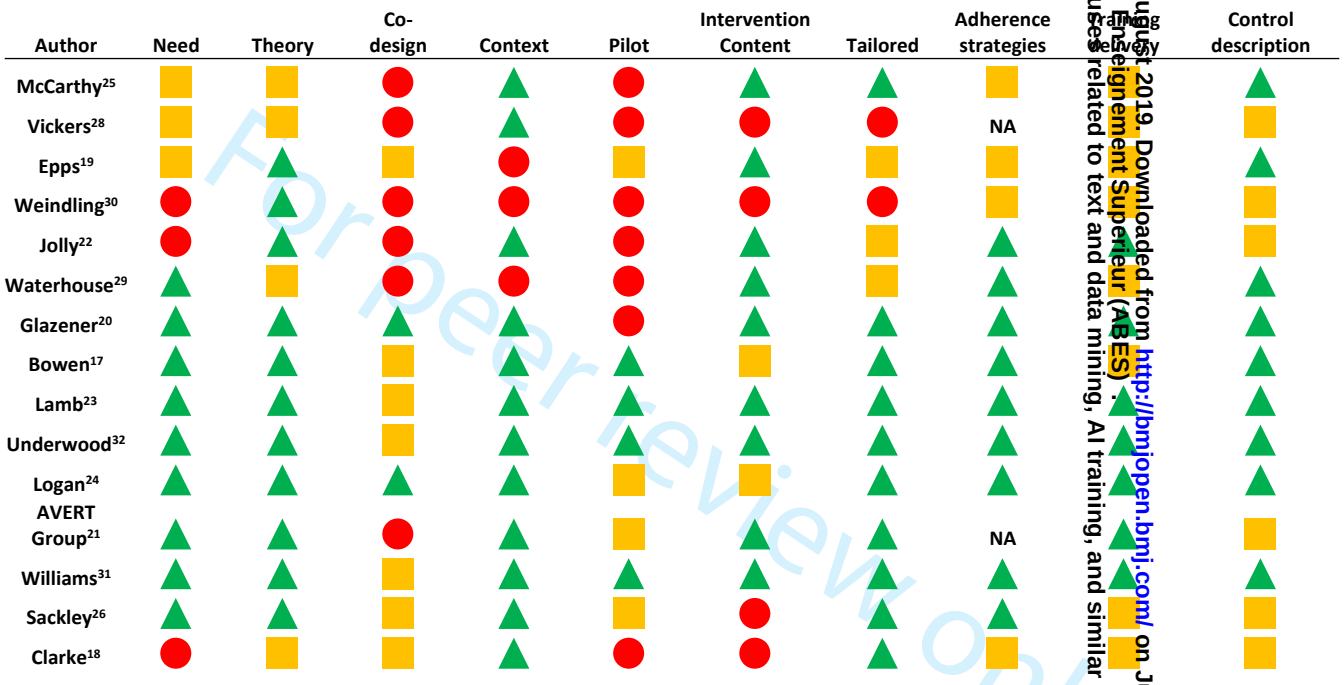
Table 2 Description of themes, subthemes and quality ratings with examples

| Theme | Sub-theme | Description of rating | Examples of data supporting rating | Rating |
|---|---|---|---|---|
| **Preparatory work** | **Need for the study** | Multiple sources of evidence of need for the study e.g. recent systematic review, guidelines, high level reports, commissioned research, national audit | International task force highlighted lack of evidence and need for evaluation. Cochrane review drew similar conclusions. | ▲ |
| | | Single source of evidence / non-systematic review to support need for study | Old systematic review indicates paucity of high quality research. | ■ |
| | | Lack of clarity or underpinning evidence regarding need for study | Poor justification for this study. Evidence cited doesn't support the need for this particular study. | ● |
| | **Theoretical underpinning** | Theoretical underpinning described | Physiological and psychological theories underpinning the intervention described in detail. | ▲ |
| | | Lacks clear theoretical underpinning | No information provided regarding the theoretical basis for the intervention provided. | ■ |
| | **Co-design** | Good PPI and expert clinical input | Patients and clinicians helped develop the intervention. | ▲ |
| | | Good PPI but weak or no expert clinical input / Good clinical input but unclear or no PPI | Clinicians contributed to the intervention development but no indication of service user involvement. | ■ |
| | | No co-design | No co-design was undertaken to develop the intervention. | ● |
| | **Contextual considerations** | Context considered | The use of different professionals in delivering the intervention reflected the real world situation of how this would occur in practice. | ▲ |
| | | Context not adequately considered | There was a lack of understanding of relevant context and factors needed for intervention development and delivery. | ● |
| | **Piloting of intervention** | Pilot conducted, evaluated and findings addressed for main evaluation | The pilot data helped refine the intervention for evaluation in the main trial. | ▲ |
| | | Pilot conducted but findings not clearly addressed in intervention for main evaluation | The pilot work led to a modification of the control intervention but unclear as to whether this also happened for the novel intervention. | ■ |
| | | No pilot reported | No piloting of intervention reported | ● |

| | | | | |
|---|---|---|---|---|
| **Intervention and control** | **Content and dose** | Intervention components and dose clearly described | The content and the dose of the exercise programme was described in detail. | ▲ |
| | | Intervention components clearly described but dose was not standardised | The content of the programme was well described but no specific dose was prescribed. | ■ |
| | | Intervention not replicable from description of components and dose | Intervention was based on usual practice and had no protocol or guidance on minimum dose. | ● |
| | **Tailoring** | Formalised assessment to inform tailoring | An assessment tool was used to determine the individuals level of exercise intensity | ▲ |
| | | Clinical judgement only used to inform tailoring | Therapists used their clinical judgement to individually tailor programmes. | ■ |
| | | Not adequately reported | Intervention individually tailored but no information as to how this was undertaken. | ● |
| | **Adherence support strategies** | Explicit strategies to support adherence to the intervention clearly reported | Specific adherence strategies described as part of the intervention. | ▲ |
| | | No clear information regarding adherence support strategies | No information reported regarding adherence strategies. | ● |
| | | Supporting adherence is not relevant to the intervention | The intervention was passive and adherence strategies not relevant. | NA |
| | **Intervention training** | Standardised training in intervention received +/- additional/ongoing support or training | Staff attended a 1.5 day training session and had an additional support session with ongoing contact from research team. | ▲ |
| | | No standardised intervention training received but staff delivering described to be experienced in the intervention or training of staff unclear/not reported | Staff have post graduate training in the intervention but no study specific training reported. | ■ |
| | **Control description** | Active control/attention control/usual care with some standardised components | Control was an active intervention that differed from intervention only in terms of delivery setting. | ▲ |
| | | Usual care had no standardised components | Control was usual care and was not standardised between sites. | ■ |

Key: ▲ High quality ■ Some/Unclear quality ● Limited quality

Table 3 Quality of intervention development work ordered by year of publication




Key:

▲ High quality ■ Some/Unclear quality ● Limited quality

*Table 4 Joint display of treatment success ordered by quality of intervention development work*

| Author | Need | Theory | Co-design | Context | Pilot | Intervention Content | Tailored | Adherence strategies | Training delivery | Control description | Treatment success |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Lamb[23] | ▲ | ▲ | ■ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | Statistically significant in favour of intervention |
| Williams[31] | ▲ | ▲ | ■ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | Statistically significant in favour of intervention |
| Underwood[32] | ▲ | ▲ | ■ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | True negative (No difference) |
| Glazener[20] | ▲ | ▲ | ▲ | ▲ | ● | ▲ | ▲ | ▲ | ▲ | ▲ | True negative (No difference) |
| Logan[24] | ▲ | ▲ | ▲ | ▲ | ■ | ■ | ▲ | ▲ | ▲ | ▲ | True negative (No difference) |
| Bowen[17] | ▲ | ▲ | ■ | ▲ | ▲ | ■ | ▲ | ▲ | ■ | ▲ | Inconclusive in favour of intervention |
| AVERT Group[21] | ▲ | ▲ | ● | ▲ | ■ | ▲ | ▲ | NA | ▲ | ■ | Statistically significant in favour of control |
| Sackley[26] | ▲ | ▲ | ■ | ▲ | ■ | ● | ▲ | ▲ | ■ | ■ | True negative (No difference) |
| Jolly[22] | ● | ▲ | ● | ▲ | ● | ▲ | ■ | ▲ | ▲ | ■ | True negative (No difference) |
| McCarthy[25] | ■ | ■ | ● | ▲ | ● | ▲ | ▲ | ■ | ■ | ▲ | Statistically significant in favour of intervention |
| Waterhouse[29] | ▲ | ■ | ● | ● | ● | ▲ | ■ | ▲ | ■ | ▲ | True negative (No difference) |
| Epps[19] | ■ | ▲ | ■ | ● | ■ | ▲ | ■ | ■ | ■ | ▲ | Inconclusive in favour of control |
| Clarke[18] | ● | ■ | ■ | ▲ | ● | ● | ▲ | ■ | ■ | ■ | True negative (No difference) |
| Vickers[28] | ■ | ■ | ● | ▲ | ● | ● | ● | NA | ■ | ■ | Statistically significant in favour of intervention |
| Weindling[30] | ● | ▲ | ● | ● | ● | ● | ● | ■ | ■ | ■ | True negative (No difference) |

Key:

▲ High quality ■ Some/Unclear quality ● Limited quality

## DISCUSSION

Physical rehabilitation research targets a broad population although we found that studies for people with stroke to be the most common (n=4). We established that only one third (5/15) of the randomised controlled trials of physical rehabilitation funded by the NIHR HTA programme successfully demonstrated a statistically significant effect for one of the randomised groups in each trial. Four (27%) trials found an effect in favour of the 'new' intervention. Although we would not expect all studies to demonstrate effectiveness in favour of the 'new' intervention, the equipoise principle implies that there would be no difference between the proportion of studies favouring intervention or control[9]. However, this doesn't account for a null outcome. We were able to use contemporary research methods to develop an assessment of the quality of development work and assessed the included trials to be of varied quality in terms of intervention development work. In general, we found that comprehensive intervention development may have a positive relationship with treatment success. Two studies[23 31] with high quality intervention development reported treatment success although two older[25 28] and possibly less well reported trials also reported effective interventions. Developments in complex intervention evaluation[5], reporting standards[16 33] and involving patients and the public in research[34] have occurred since the inception of the HTA programme and as such some development work may have been undertaken but not reported in the older studies. A recent overview of approaches to developing interventions noted the absence of patient and public involvement[35]. In addition, there was limited evidence of piloting the intervention prior to proceeding to the full trial with only four studies reporting this having been done. Most (> 80%) drug intervention development studies fail to reach the 'Phase III' trial stage.[36] Public health interventions have tended to go straight to an RCT without piloting which may contribute to challenges in demonstrating effectiveness.[11] There are of course other factors that influence trial findings, including trial methods and conduct, however our question was specifically determined to explore what, if any, relationship existed between intervention development and outcomes and not in the effectiveness of particular interventions.

A strength of our study is the use of integrative mixed methods analysis which has enabled us to explore the relationship between development work and outcome. This rarely used approach in evidence synthesis[37] has given us a unique insight that would not have been possible using a quantitative or qualitative analysis alone. A limitation of our work could be the focus on a single UK funding stream which does not necessarily reflect the body of research funded from other sources and therefore the quality of intervention development work is not necessarily generalizable. However, the NIHR HTA programme is the single largest funder of randomised controlled trials of applied health research in the UK. They publish detailed monographs of their funded studies, along with protocols and other supporting publications that provide a detailed and rich source of data beyond what would normally be available in journal-based peer reviewed publications alone. We were able to retain the essence and nuances of the qualitative data whilst developing categorical ratings of quality to help us better explore the relationship between development work and treatment success.

Our findings are similar to those of Dent and Raftery[9] in relation to those trials showing a benefit who reported 19% (16/85) of studies found in favour of the new intervention. It has been suggested that a 50% success rate is a good investment for healthcare research,[38] however, our findings indicate that the studies we reviewed fell well below this. In contrast, we observed a considerably larger proportion of true negative studies (8/15; 53%) compared with 19/85 (22%) reported by Dent and Raftery.[9] The

difference is even greater when compared with a review of cancer trials in the USA where only 2% of trials found a true negative outcome.[10] The reasons for the differences are unclear but could include the pragmatic nature of HTA funded trials and the relative smaller effect sizes often associated with trials of rehabilitation.[39]

It has been recently suggested that RCTs should only be undertaken if they are justified both scientifically and ethically by having a clear hypothesis and established uncertainty[40] and our findings support that by way of good quality intervention development work. Our findings also align with the elements suggested to be key for developing interventions and reducing research waste by increasing the likelihood of success[41] which will form a comprehensive supplement to the development phase of the updated MRC guidance on developing and evaluating interventions due for publication in 2019. The NIHR HTA is publically funded and by increasing effort and focus on developing rehabilitation and other interventions in the future researchers and funding bodies could increase the possibility of a definitive trial reporting beneficial findings after much investment of time and public money.

## CONCLUSIONS

Despite much research effort and funding, only four out of fifteen evaluations of 'new' rehabilitation interventions funded by the NIHR HTA programme were found to be unequivocally effective. Most studies reported no difference in outcome between study arms. We have used mixed methods research to explore the relationship between intervention development work and treatment success and developed a method of assessing the quality of this work which suggests comprehensive intervention development work may have a positive relationship with treatment success.

## RECOMMENDATIONS

As this was an exploratory study, further work should be undertaken to establish the validity of quality assessment of intervention development work. This said, researchers and funding agencies should not undervalue the potential benefit of high quality intervention development work prior to definitive randomised controlled trials to reduce the likelihood of a null outcome and improve current rates of treatment success.

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## COMPETING INTERESTS

None

## DATA SHARING STATEMENT

No additional data are available.

## AUTHOR CONTRIBUTION

VG: Conception and design, data collection, analysis and interpretation, drafting and approving the manuscript;

JH: Design, data collection, analysis and interpretation, drafting and approving the manuscript;

JF: Data collection, analysis, revising and approving the manuscript;

KF: Data collection, revising and approving the manuscript;

CP: Data collection, revising and approving the manuscript;

DR: Conception, revising and approving the manuscript.

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**Figure Legends:**

Figure 1 Study selection

Figure 2 Classification of Primary Outcome

Figure 3 Treatment success of included trials based on 95% Confidence Intervals and Minimum Clinically Important Difference from sample size calculation (d)

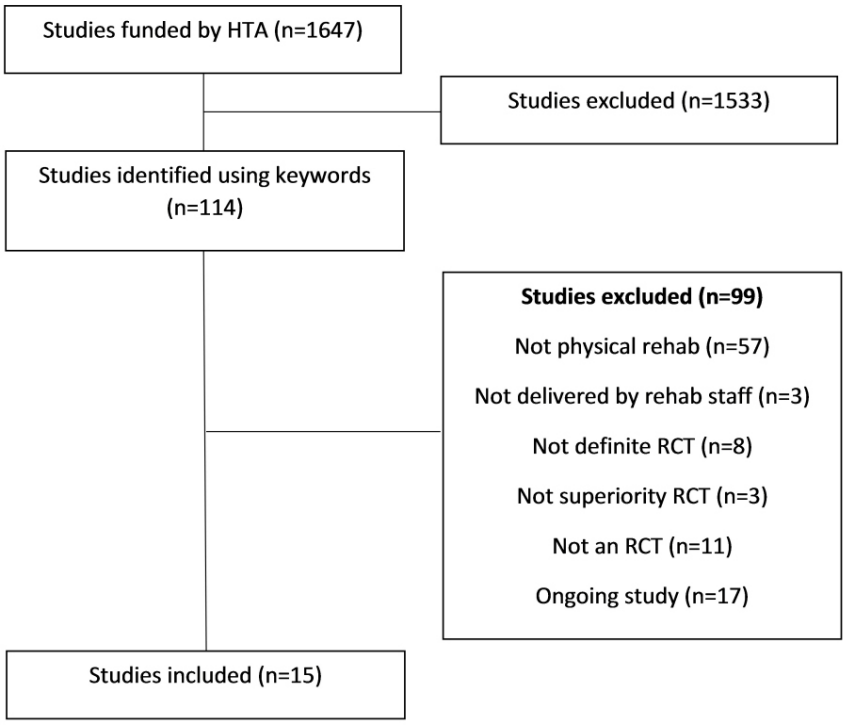


Figure 1 Study selection

Figure 1 Study selection

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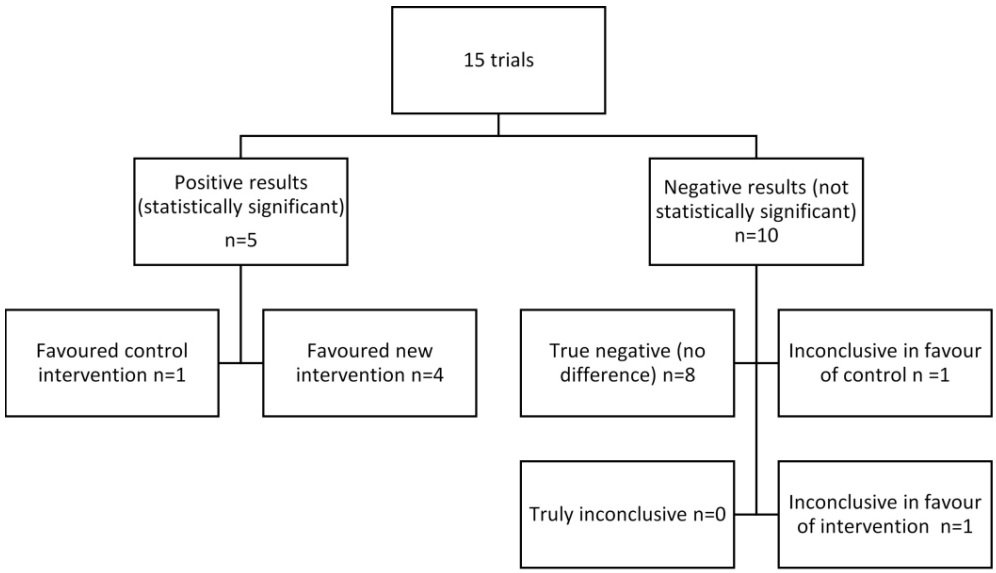


Figure 2 Classification of primary outcome

Figure 2 Classification of Primary Outcome

89x66mm (300 x 300 DPI)

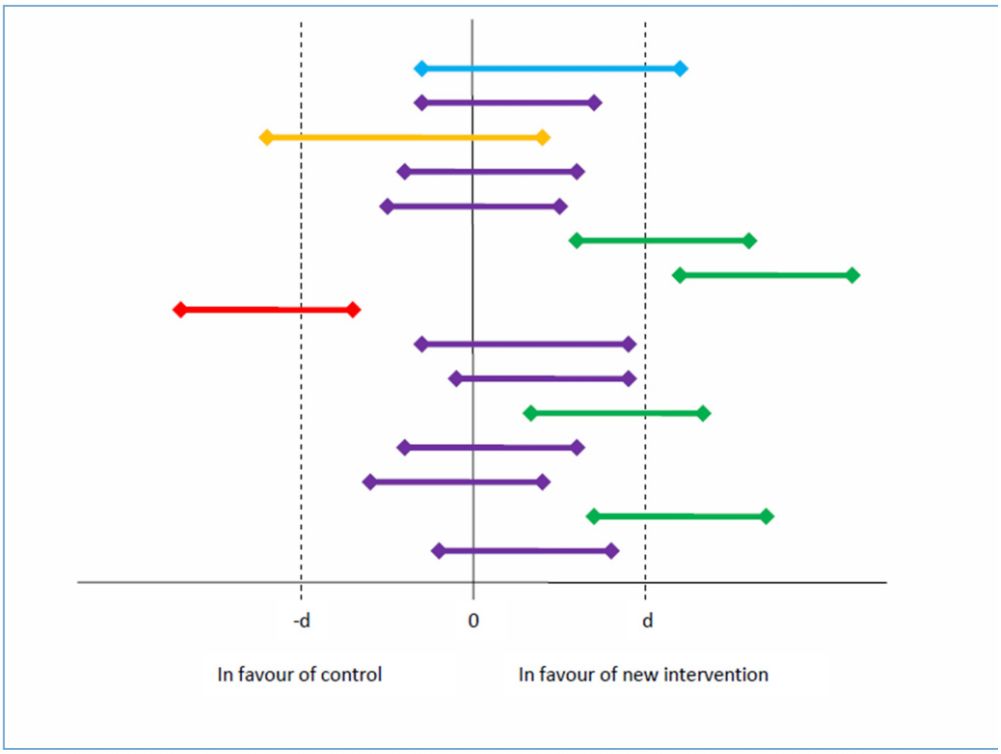


Figure 3 Treatment success of included trials based on 95% Confidence Interval and Minimal Clinically Important Difference from trial sample size calculation (d)

Key: *Green = statistically significantly in favour of intervention; Red = statistically significantly in favour of control; Blue = Inconclusive in favour of intervention; Yellow = Inconclusive in favour of control; Purple = True negative (no difference)*

Figure 3 Treatment success of included trials based on 95% Confidence Interval and Minimal Clinically Important Difference from trial sample size calculation (d)

87x89mm (300 x 300 DPI)

BMJ Open

# Intervention development and treatment success in UK Health Technology Assessment funded trials of physical rehabilitation: a mixed methods analysis



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| Primary Subject Heading: | Health services research |
| Secondary Subject Heading: | Rehabilitation medicine |
| Keywords: | rehabilitation, intervention development, mixed methods, randomised controlled trials |
| | |

# Intervention development and treatment success in UK Health Technology Assessment funded trials of physical rehabilitation: a mixed methods analysis

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**Keywords**

Rehabilitation, randomised controlled trials, quality, intervention development, mixed methods

## Abstract

**Objectives:** Physical rehabilitation is a complex process and trials of rehabilitation interventions are increasing in number but often report null results. This study aimed to establish treatment success rates in physical rehabilitation trials funded by the National Institute of Health Research Health Technology Assessment (NIHR HTA) programme and examine any relationship between treatment success and the quality of intervention development work undertaken.

**Design:** Mixed methods study

**Setting:** UK

**Methods:**

The NIHR HTA portfolio was searched for all completed definitive randomised controlled trials of physical rehabilitation interventions from inception to July 2016. Treatment success was categorised according to criteria developed by Djulbegovic and colleagues. Detailed textual data regarding any intervention development work were extracted from trial reports and supporting publications and informed the development of quality ratings. Mixed methods integrative analysis was undertaken to explore the relationship between quantitative and qualitative data using joint displays.

**Results:** Fifteen trials were included in the review. Five reported a definitive finding, four of which were in favour of the 'new' intervention. Eight trials reported a true negative (no difference) outcome. Integrative analysis indicated those with lower quality intervention development work were less likely to report treatment success.

**Conclusions:** Despite much effort and funding, most physical rehabilitation trials report equivocal findings. Greater focus on high quality intervention development may reduce the likelihood of a null result in the definitive trial, alongside high quality trial methods and conduct.

**Strengths and limitations of this study:**

- To our knowledge, this study is the first to use mixed methods integrative analyses to explore the relationship between quality of intervention development work and treatment success.
- Using the NIHR HTA Journal monographs, published protocols and other supporting publications for each study together provided a detailed and rich source of data beyond what would be found in a single traditional journal publication.
- The study reviewed randomised controlled trials of physical rehabilitation from a single UK funder as an exemplar and therefore findings may not be representative of other complex interventions or other funding bodies.

## BACKGROUND

Rehabilitation is *"a set of interventions designed to optimise function and reduce disability in individuals with health conditions in interaction with their environment".*[1] and is an essential aspect of healthcare provision. By its very nature rehabilitation in clinical practice is an individually focused, complex activity, involving interventions that are multi-faceted and often implicit in nature[2] and as such, historically, this has been viewed as a barrier to undertaking research.[3] This said, there is a growing body of randomised controlled trials (RCTs) of rehabilitation, suggesting that these challenges can be overcome.[4] This may, in part, be supported by the publication of the Medical Research Council (MRC) Framework for developing and evaluating complex interventions.[5 6]

The MRC framework was developed to optimise the likelihood that new interventions are not rejected as being ineffective when inadequate effort has been made in the development of the intervention.[7] Likewise, Chalmers and Glasziou[8] highlighted the importance of avoiding research waste and recommended that sufficient effort is made to ensure the relevant research questions are identified and addressed using high quality research methods. However, there appears to have been no formal evaluation of the impact of using the development component of the framework on trial outcomes and whether we are observing evidence of effective interventions being developed.

Previous UK[9] and USA[10] reviews synthesised successful and non-successful treatment outcomes from trials of new interventions in order to assess the equipoise principle and to understand what return has been achieved on the investment made by those taking part in the trials, researchers and funders. Dent and Raftery[9] reported 24% (20/85) primary outcome comparisons as having a positive result, of which 16/85 (19%) were in favour of the new intervention, with 19/85 (22%) comparisons reporting a true negative outcome. However, these authors did not focus on rehabilitation interventions, nor did they seek to understand factors that may impact on treatment success, such as the quality or intensity of intervention development pre-trial procedures. Informal discussions with colleagues in the UK and internationally noted that an increasing number of publically funded, large RCTs evaluating physical rehabilitation interventions had reported null findings. Similar concerns have been reported in studies of public health interventions.[11 12] Our study, therefore, sought to assess this observation and also explore whether intervention development activities contributed to treatment success using the National Institute of Health Research Health Technology Assessment programme (NIHR HTA) as an exemplar.

We aimed to use data from the NIHR HTA to:

(a) Establish the treatment outcomes of funded RCTs of physical rehabilitation;

(b) Establish how many new interventions were found to be effective;

(c) Examine what work had been done in terms of developing the new intervention;

(d) Examine the relationship between (a) and (c).

We adopted a mixed methods approach to address the study aims. Although evidence of using integrative mixed methods approaches in synthesising evidence on complex interventions is limited, mixing together qualitative and quantitative data can generate understanding that has the potential to be greater than the sum of the individual parts.[13]

## METHODS

### Design

We undertook a review of NIHR HTA funded randomised controlled trials of physical rehabilitation interventions using narrative synthesis of outcomes and mixed methods analysis of the relationship between intervention development and categorical treatment outcomes using joint displays.

### *Patient and Public Involvement*

Patients and the public were not involved in this study.

### *Data sources and inclusion criteria*

We included superiority randomised controlled trials of physical rehabilitation funded by the NIHR HTA programme. The interventions could be delivered by a single profession or be multi-professional. The NIHR HTA programme is the leading public funding source for randomised controlled trials (RCTs) in the UK and trials of rehabilitation are increasingly part of the portfolio. We only included completed RCTs whose main trial findings were reported in an HTA monograph or peer-reviewed publication in order to establish treatment success. We excluded: pilot and feasibility RCTs as they do not aim to assess the efficacy or effectiveness of interventions;[14] studies where the interventions were primarily psychological or cognitive as the focus of the study was physical rehabilitation; where the primary outcome findings were not reported with a 95% confidence interval (CI) as these data were required to assess treatment success.

### *Search and screening*

We searched the HTA Project Portfolio (since superseded by the NIHR Journals Library https://www.journalslibrary.nihr.ac.uk/#/) from inception to July 2016 using the following keywords: physiotherap*OR occupational therap* OR speech and language therap* OR rehabilitation. We removed duplicates and then titles and scientific abstracts were reviewed for potential inclusion by one person and checked by a second. Subsequently full text reports were screened for inclusion by one person and checked by a second. Any disagreements were discussed and agreed with a third person.

### *Data extraction*

All data were extracted by one person and checked by a second. Discrepancies were discussed and resolved with a third person.

*Quantitative Trial data:* Data extracted from each trial publication included trial design, target population, health categories (using the Health Research Classification System), primary outcome(s) and time point, minimal important clinical difference (MCID) or percentage change that the trial aimed to detect, planned and achieved sample size, and primary outcome results with 95% CI. We also recorded the professional background of the Chief Investigator and amount of funding awarded.

*Qualitative Intervention development data*: Using the revised version of Criteria for Reporting the Development and Evaluation of Complex Interventions (CReDECI 2)[15] and the Template for Intervention Description and Replication checklist (TIDieR)[16] as frameworks we extracted all available

documentary (qualitative) data from the body of the text regarding intervention development, including descriptions of underlying theory, intervention components and reasons for selection, intended interactions between components, contextual considerations, piloting of intervention and impact of definitive intervention to be evaluated, control components, planned intervention delivery and materials. Where additional supporting publications were cited, such as a protocol or intervention development studies, we used these as additional sources of documentary data.

**Data analysis**

We used summary statistics to describe the characteristics of the included studies. We categorised primary outcome findings into one of six treatment outcome categories as described by Djulbegovic and colleagues,[10] these being: 1) statistically significant in favour of the new treatment, 2) statistically significant in favour of the control treatment 3) true negative, 4) truly inconclusive, 5) inconclusive in favour of new treatment or 6) inconclusive in favour of the control treatment. This was achieved by comparing the 95% confidence interval for the difference in primary outcome to the difference specified in the sample size calculation.[9] If the 95% confidence interval excluded a meaningful difference in either direction, implying the treatments have similar effects, the results were categorised as true negative. If the 95% confidence interval included a meaningful difference in either direction (i.e. trial failed to answer the primary question), the results were categorised as being truly inconclusive.

Where a single primary outcome and primary time point were not explicitly identified we utilised the following hierarchy to determine which primary outcome would be used in the analysis:

- Explicitly defined primary outcome
- Outcome used in power calculation
- Main outcome stated in trial objectives
- First outcome reported in sample size calculation

If a primary time point was not reported we used the first follow up time point as this is when we would expect the intervention to have had the greatest effect.

Our preliminary analysis of the qualitative documentary data involved the reading and re-reading of source documents and the extracted descriptions to consolidate our understanding of the development work undertaken in each study. Using a reflective and iterative process we undertook thematic analysis to distil, structure and make sense of intervention development activity by coding and organising data into themes and subthemes. Each theme and sub-theme provided a coherent description of the development work undertaken for each study, which were then synthesised into short descriptors to allow us to produce summary tables. The summary tables comprised a row for each study with columns for each theme and, where relevant, each subtheme. A second researcher checked, discussed and refined descriptors to ensure accuracy. From these descriptions we then developed descriptive ratings on the quality of the intervention development. Depending on the nature of the data, ratings were categorised and the iterative process involved two researchers refining and checking ratings to ensure they reflected the summary data from each study. In order to provide a visual representation of the quality of intervention development work these ratings were then converted to a quality coding to indicate high quality, some or unclear quality or limited quality. For example under co-design the highest quality rating was given when the intervention was co-

designed with *both* clinical and service user input, a middle rating when *either* clinicians or service users were involved, and the lowest quality rating when *neither* clinicians nor service users were involved.

To examine the relationship between intervention development and treatment success, we applied mixed methods analytical techniques in novel ways. For each study, we combined ratings derived from the qualitative data on intervention development with the quantitative data on treatment outcomes in a joint display.

## RESULTS

We included fifteen RCTs (Figure 1),[17-31] of which thirteen used a two-arm, parallel RCT design, one was a two-arm cluster RCT and one was a four-arm factorial design (of which only two arms related to physical rehabilitation). Table 1 provides a summary of the population, intervention, control and outcomes for each study. The combined sample size required to demonstrate a true difference in primary outcomes (excluding any inflation to account for loss to follow up) was 7548 participants. The total number of participants who provided primary outcome data was higher than this (n=7834), likely due to lower loss to follow up that estimated, although three studies[19 29 30] were considerably below their target sample size at the primary time point. Five primary outcomes were symptom-based or clinical outcomes, seven were functional measures, two were combined measures and one assessed quality of life. Primary time points varied from immediately post-intervention to one year (median 6 months). The health categories were: Stroke (n=4), Neurological conditions (n=2), Inflammatory/Immune system disorders (n=2), Respiratory (n=1), Musculoskeletal (n=1), Cardiovascular (n=1), Mental Health (n=1), Accident/injuries (n=1), Renal/urogenital (n=1) and other (n=1). Seven interventions were delivered by physiotherapists, one by occupational therapists, one by speech and language therapists, one by nurses, two could be delivered by either a physiotherapist or a nurse, two could be delivered by a physiotherapist or an occupational therapist and one was delivered by both a physiotherapist and an occupational therapist. The Chief Investigators leading the studies were physicians (n=7), physiotherapists (n=5), occupational therapists (n=1), psychologists (n=1) and methodologists (n=1). The total amount of research funding awarded was £12,515,823.

One third of studies (5/15) reported a definitive finding in favour of one of the treatment arms - four studies in favour of the new treatment, one in favour of the control. Of those with negative results, eight studies reported a true negative (no difference) outcome, one was inconclusive in favour of the new treatment, and one inconclusive in favour of the control treatment (Figures 2 and 3).

Qualitative data informed two themes and ten sub-themes which enabled us to develop data-driven quality ratings:

1. *Preparatory work* (Need for the study, underpinning theory for the intervention, co-design, context considerations and intervention piloting)
2. *Intervention and control* (Intervention content and dose, individual tailoring, adherence strategies, standardised training, control content and dose)

Table 2 provides examples of summary data underpinning each rating with Table 3 describing the quality rating for each study in chronological order. Table 4 presents the integrative qualitative and

quantitative analysis using a joint display. No single study was deemed to be high quality in each sub-theme. This said, the two best rated studies reported only expert clinical input into co-designing the intervention with a lack of clear patient and public involvement, however, they reported a definitive trial outcome in favour of the new intervention. There does not appear to be a single aspect of intervention development driving study outcomes. This said, those with lower quality development work appear more likely to show no difference in outcomes compared with those with higher quality development work. Some areas of intervention development appear to be improving with time, these being articulating a clear need and theoretical underpinning, co-design, piloting and descriptions of intervention and control components.

Table 1 Summary of included studies

| Author (year published) | Funding awarded (£) | Population (target sample size/number of participants with primary outcome data) | Intervention | Control | Primary Outcome (MCID or % change study aimed to detect) |
|---|---|---|---|---|---|
| McCarthy et al (2004) | 218,517 | People with knee osteoarthritis (n=152/200) | Twice weekly exercise group for 8 weeks plus home exercises | Home exercises | Aggregate Locomotor Function score (4 seconds) |
| Vickers et al (2004) | 161,532 | People with chronic headache (n=288/301) | Up to 12 acupuncture treatments plus usual care | Usual care from General Practitioner | Weekly headache score (35% reduction) |
| Epps et al (2005) | 152,011 | Children with juvenile arthritis (n=200/74) | 8 hydrotherapy and 8 land based sessions over 2 weeks followed by weekly/fortnightly hydrotherapy for 2 months | 16 land based exercise sessions over 2 weeks followed by weekly or fortnightly land based exercise sessions | Disease status calculated from Childhood Health Assessment Questionnaire (CHAQ), physicians' global assessment of disease activity, parents' global assessment of overall well-being, number of joints with limited ROM, number of active joints, erythrocyte sedimentation rate (30% improvement on 3 measures with < 30% deterioration on remaining 3 measures) |
| Weindling et al (2007) | 334,093 | Children with cerebral palsy (n=153/76) | Regular physiotherapy (usual care) plus additional weekly session from physiotherapy assistant for 6 months | Usual care (regular physiotherapy) | Gross Motor Function Measure (14 points) |
| Jolly et al (2007) | 480,612 | People with myocardial infarction or revascularisation (n=450/487) | Home-based self-help manual plus up to 3 face to face and 1 phone call support over 12 weeks | Centre-based cardiac rehabilitation | Incremental shuttle walk test (6 shuttles); Hospital anxiety and depression scale (1.5 points); smoking cessation (20%); blood pressure (6mmHg systolic); serum cholesterol (0.4 mmol/l) |
| Waterhouse et al (2010) | 460,543 | People with Chronic Obstructive Pulmonary Disease (n=372/162) | Twice weekly community-based pulmonary rehabilitation | Twice weekly hospital-based pulmonary rehabilitation | Endurance Shuttle Walk Test (60% increase in distance walked) |
| Glazener et al (2011) | 1,051,699 | Men with incontinence post-prostate surgery (696/788) | Assessment and treatment and exercise over 4 face to face sessions plus advice leaflet | Advice leaflet | Self-reported urinary incontinence (15% reduction in % of people with urinary incontinence) |
| Bowen et al (2012) | 1,457,533 | Adults with aphasia or dysarthria after stroke (n=170/153) | Speech and language therapy visits up to 3 sessions per week for up to 16 weeks | Volunteer visits up to 3 sessions per week for up to 16 weeks | Therapy Outcome measure (0.5) |
| Lamb et al (2012) | 755,310 | People with whiplash with persistent symptoms (n=422/507) | 6 sessions of assessment and treatment/exercise over 8 weeks | Single session of advice | Neck Disability Index (3 points) |
| Underwood et al (2013) | 1,957,884 | Care home residents (n=409/493) | Twice weekly exercise group for a year | Depression awareness training for care home staff | Geriatric Depression Scale (17.3% reduction in % of people with depression) |
| Logan et al (2014) | 993,080 | People with stroke (n=440/503) | Up to 12 therapy visits to increase outdoor mobility plus verbal/written advice | Verbal/written advice | SF-36 Social function domain (12.5 points) |
| Williams et al (2015) | 976,955 | People with rheumatoid arthritis (n=352/438) | 6 sessions of exercise plus home exercises over 12 weeks | Single assessment advice session with 2 further optional sessions over 12 weeks (no exercises) | Michigan Hand Outcome Questionnaire (0.3) |
| AVERT Group (2015) | 282,372 | People with stroke (n=2104/2083) | 3 additional out of bed sessions per day for up to 2 weeks | Usual care | Modified Rankin Scale-(mRS) (7.1% Absolute risk reduction of a mRS score of 3-6) |

| | | | | | |
|---|---|---|---|---|---|
| Sackley et al (2016) | 1,797,676 | Care home residents with stroke (n=660/870) | Individualised occupational therapy | No occupational therapy | Barthel Index (2 points) |
| Clarke et al (2016) | 1,436,006 | People with Parkinson's (n=680/699) | Up to 8 individualised sessions of Physiotherapy and up to 8 individualised sessions of occupational therapy | No therapy | Nottingham Extended Activities of Daily Living (2.5 points) |

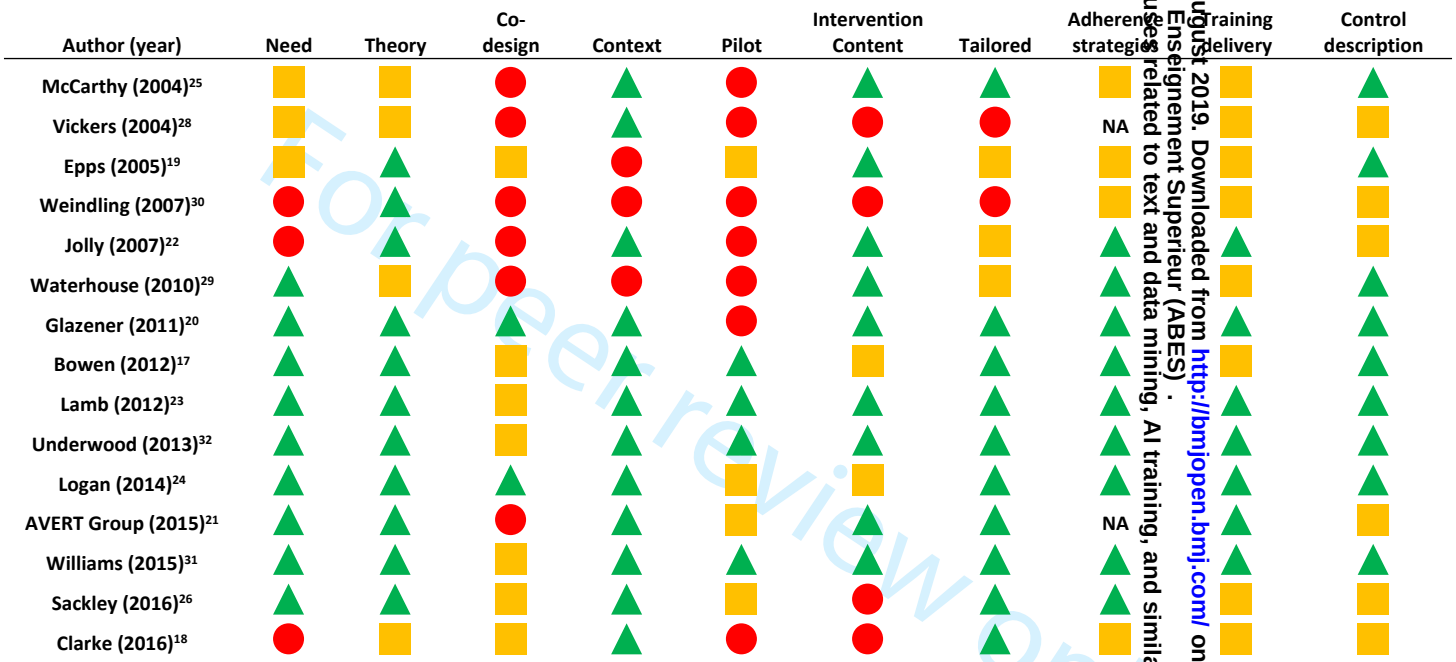
Table 2 Description of themes, subthemes and quality ratings with examples

| Theme | Sub-theme | Description of rating | Examples of data supporting rating | Rating |
|---|---|---|---|---|
| **Preparatory work** | **Need for the study** | Multiple sources of evidence of need for the study e.g. recent systematic review, guidelines, high level reports, commissioned research, national audit | International task force highlighted lack of evidence and need for evaluation. Cochrane review drew similar conclusions. | ▲ |
| | | Single source of evidence / non-systematic review to support need for study | Old systematic review indicates paucity of high quality research. | ■ |
| | | Lack of clarity or underpinning evidence regarding need for study | Poor justification for this study. Evidence cited doesn't support the need for this particular study. | ● |
| | **Theoretical underpinning** | Theoretical underpinning described | Physiological and psychological theories underpinning the intervention described in detail. | ▲ |
| | | Lacks clear theoretical underpinning | No information provided regarding the theoretical basis for the intervention provided. | ■ |
| | **Co-design** | Good PPI and expert clinical input | Patients and clinicians helped develop the intervention. | ▲ |
| | | Good PPI but weak or no expert clinical input / Good clinical input but unclear or no PPI | Clinicians contributed to the intervention development but no indication of service user involvement. | ■ |
| | | No co-design | No co-design was undertaken to develop the intervention. | ● |
| | **Contextual considerations** | Context considered | The use of different professionals in delivering the intervention reflected the real world situation of how this would occur in practice. | ▲ |
| | | Context not adequately considered | There was a lack of understanding of relevant context and factors needed for intervention development and delivery. | ● |
| | **Piloting of intervention** | Pilot conducted, evaluated and findings addressed for main evaluation | The pilot data helped refine the intervention for evaluation in the main trial. | ▲ |
| | | Pilot conducted but findings not clearly addressed in intervention for main evaluation | The pilot work led to a modification of the control intervention but unclear as to whether this also happened for the novel intervention. | ■ |
| | | No pilot reported | No piloting of intervention reported | ● |

| | | | | |
|---|---|---|---|---|
| **Intervention and control** | **Content and dose** | Intervention components and dose clearly described | The content and the dose of the exercise programme was described in detail. | ▲ |
| | | Intervention components clearly described but dose was not standardised | The content of the programme was well described but no specific dose was prescribed. | ■ |
| | | Intervention not replicable from description of components and dose | Intervention was based on usual practice and had no protocol or guidance on minimum dose. | ● |
| | **Tailoring** | Formalised assessment to inform tailoring | An assessment tool was used to determine the individuals level of exercise intensity | ▲ |
| | | Clinical judgement only used to inform tailoring | Therapists used their clinical judgement to individually tailor programmes. | ■ |
| | | Not adequately reported | Intervention individually tailored but no information as to how this was undertaken. | ● |
| | **Adherence support strategies** | Explicit strategies to support adherence to the intervention clearly reported | Specific adherence strategies described as part of the intervention. | ▲ |
| | | No clear information regarding adherence support strategies | No information reported regarding adherence strategies. | ● |
| | | Supporting adherence is not relevant to the intervention | The intervention was passive and adherence strategies not relevant. | NA |
| | **Intervention training** | Standardised training in intervention received +/- additional/ongoing support or training | Staff attended a 1.5 day training session and had an additional support session with ongoing contact from research team. | ▲ |
| | | No standardised intervention training received but staff delivering described to be experienced in the intervention or training of staff unclear/not reported | Staff have post graduate training in the intervention but no study specific training reported. | ■ |
| | **Control description** | Active control/attention control/usual care with some standardised components | Control was an active intervention that differed from intervention only in terms of delivery setting. | ▲ |
| | | Usual care had no standardised components | Control was usual care and was not standardised between sites. | ■ |

Key: ▲ High quality ■ Some/Unclear quality ● Limited quality

Table 3 Quality of intervention development work ordered by year of publication




Key:

High quality  Some/Unclear quality  Limited quality

*Table 4 Joint display of treatment success ordered by quality of intervention development work*

| Author | Need | Theory | Co-design | Context | Pilot | Intervention Content | Tailored | Adherence strategies | Training delivery | Control description | Treatment success |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Lamb[23] | ▲ | ▲ | ■ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | Statistically significant in favour of intervention |
| Williams[31] | ▲ | ▲ | ■ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | Statistically significant in favour of intervention |
| Underwood[32] | ▲ | ▲ | ■ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | True negative (No difference) |
| Glazener[20] | ▲ | ▲ | ▲ | ▲ | ● | ▲ | ▲ | ▲ | ▲ | ▲ | True negative (No difference) |
| Logan[24] | ▲ | ▲ | ▲ | ▲ | ■ | ■ | ▲ | ▲ | ▲ | ▲ | True negative (No difference) |
| Bowen[17] | ▲ | ▲ | ■ | ▲ | ▲ | ■ | ▲ | ▲ | ■ | ▲ | Inconclusive in favour of intervention |
| AVERT Group[21] | ▲ | ▲ | ● | ▲ | ■ | ▲ | ▲ | NA | ▲ | ■ | Statistically significant in favour of control |
| Sackley[26] | ▲ | ▲ | ■ | ▲ | ■ | ● | ▲ | ▲ | ■ | ■ | True negative (No difference) |
| Jolly[22] | ● | ▲ | ● | ▲ | ● | ▲ | ■ | ▲ | ▲ | ■ | True negative (No difference) |
| McCarthy[25] | ■ | ■ | ● | ▲ | ● | ▲ | ▲ | ■ | ■ | ▲ | Statistically significant in favour of intervention |
| Waterhouse[29] | ▲ | ■ | ● | ● | ● | ▲ | ■ | ▲ | ■ | ▲ | True negative (No difference) |
| Epps[19] | ■ | ▲ | ■ | ● | ■ | ▲ | ■ | ■ | ■ | ▲ | Inconclusive in favour of control |
| Clarke[18] | ● | ■ | ■ | ▲ | ● | ● | ▲ | ■ | ■ | ■ | True negative (No difference) |
| Vickers[28] | ■ | ■ | ● | ▲ | ● | ● | ● | NA | ■ | ■ | Statistically significant in favour of intervention |
| Weindling[30] | ● | ▲ | ● | ● | ● | ● | ● | ■ | ■ | ■ | True negative (No difference) |

Key:

▲ High quality ■ Some/Unclear quality ● Limited quality

## DISCUSSION

Physical rehabilitation research targets a broad population although we found that studies for people with stroke to be the most common (n=4). We established that only one third (5/15) of the randomised controlled trials of physical rehabilitation funded by the NIHR HTA programme successfully demonstrated a statistically significant effect for one of the randomised groups in each trial. Four (27%) trials found an effect in favour of the 'new' intervention. Although we would not expect all studies to demonstrate effectiveness in favour of the 'new' intervention, the equipoise principle implies that there would be no difference between the proportion of studies favouring intervention or control[9]. However, this doesn't account for a null outcome. We were able to use contemporary research methods to develop an assessment of the quality of development work and assessed the included trials to be of varied quality in terms of intervention development work. In general, we found that comprehensive intervention development may have a positive relationship with treatment success. Two studies[23 31] with high quality intervention development reported treatment success although two older[25 28] and possibly less well reported trials also reported effective interventions. Developments in complex intervention evaluation[5], reporting standards[16 33] and involving patients and the public in research[34] have occurred since the inception of the HTA programme and as such some development work may have been undertaken but not reported in the older studies. A recent overview of approaches to developing interventions noted the absence of patient and public involvement[35]. In addition, there was limited evidence of piloting the intervention prior to proceeding to the full trial with only four studies reporting this having been done. Most (> 80%) drug intervention development studies fail to reach the 'Phase III' trial stage.[36] Public health interventions have tended to go straight to an RCT without piloting which may contribute to challenges in demonstrating effectiveness.[11] There are of course other factors that influence trial findings, including trial methods and conduct, however our question was specifically determined to explore what, if any, relationship existed between intervention development and outcomes and not in the effectiveness of particular interventions.

A strength of our study is the use of integrative mixed methods analysis which has enabled us to explore the relationship between development work and outcome. This rarely used approach in evidence synthesis[37] has given us a unique insight that would not have been possible using a quantitative or qualitative analysis alone. A limitation of our work could be the focus on a single UK funding stream which does not necessarily reflect the body of research funded from other sources and therefore the quality of intervention development work is not necessarily generalizable. However, the NIHR HTA programme is the single largest funder of randomised controlled trials of applied health research in the UK. They publish detailed monographs of their funded studies, along with protocols and other supporting publications that provide a detailed and rich source of data beyond what would normally be available in journal-based peer reviewed publications alone. We were able to retain the essence and nuances of the qualitative data whilst developing categorical ratings of quality to help us better explore the relationship between development work and treatment success.

Our findings are similar to those of Dent and Raftery[9] in relation to those trials showing a benefit who reported 19% (16/85) of studies found in favour of the new intervention. It has been suggested that a 50% success rate is a good investment for healthcare research,[38] however, our findings indicate that the studies we reviewed fell well below this. In contrast, we observed a considerably larger proportion of true negative studies (8/15; 53%) compared with 19/85 (22%) reported by Dent and Raftery.[9] The

difference is even greater when compared with a review of cancer trials in the USA where only 2% of trials found a true negative outcome.[10] The reasons for the differences are unclear but could include the pragmatic nature of HTA funded trials and the relative smaller effect sizes often associated with trials of rehabilitation.[39]

It has been recently suggested that RCTs should only be undertaken if they are justified both scientifically and ethically by having a clear hypothesis and established uncertainty[40] and our findings support that by way of good quality intervention development work. Our findings also align with the elements suggested to be key for developing interventions and reducing research waste by increasing the likelihood of success[41] which will form a comprehensive supplement to the development phase of the updated MRC guidance on developing and evaluating interventions due for publication in 2019. The NIHR HTA is publically funded and by increasing effort and focus on developing rehabilitation and other interventions in the future researchers and funding bodies could increase the possibility of a definitive trial reporting beneficial findings after much investment of time and public money.

## CONCLUSIONS

Despite much research effort and funding, only four out of fifteen evaluations of 'new' rehabilitation interventions funded by the NIHR HTA programme were found to be unequivocally effective. Most studies reported no difference in outcome between study arms. We have used mixed methods research to explore the relationship between intervention development work and treatment success and developed a method of assessing the quality of this work which suggests comprehensive intervention development work may have a positive relationship with treatment success.

## RECOMMENDATIONS

As this was an exploratory study, further work should be undertaken to establish the validity of quality assessment of intervention development work. This said, researchers and funding agencies should not undervalue the potential benefit of high quality intervention development work prior to definitive randomised controlled trials to reduce the likelihood of a null outcome and improve current rates of treatment success.

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## COMPETING INTERESTS

None

## DATA SHARING STATEMENT

No additional data are available.

## AUTHOR CONTRIBUTION

VG: Conception and design, data collection, analysis and interpretation, drafting and approving the manuscript;

JH: Design, data collection, analysis and interpretation, drafting and approving the manuscript;

JF: Data collection, analysis, revising and approving the manuscript;

KF: Data collection, revising and approving the manuscript;

CP: Data collection, revising and approving the manuscript;

DR: Conception, revising and approving the manuscript.

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**Figure Legends:**

Figure 1 Study selection

Figure 2 Classification of Primary Outcome

Figure 3 Treatment success of included trials based on 95% Confidence Intervals and Minimum Clinically Important Difference from sample size calculation (d)

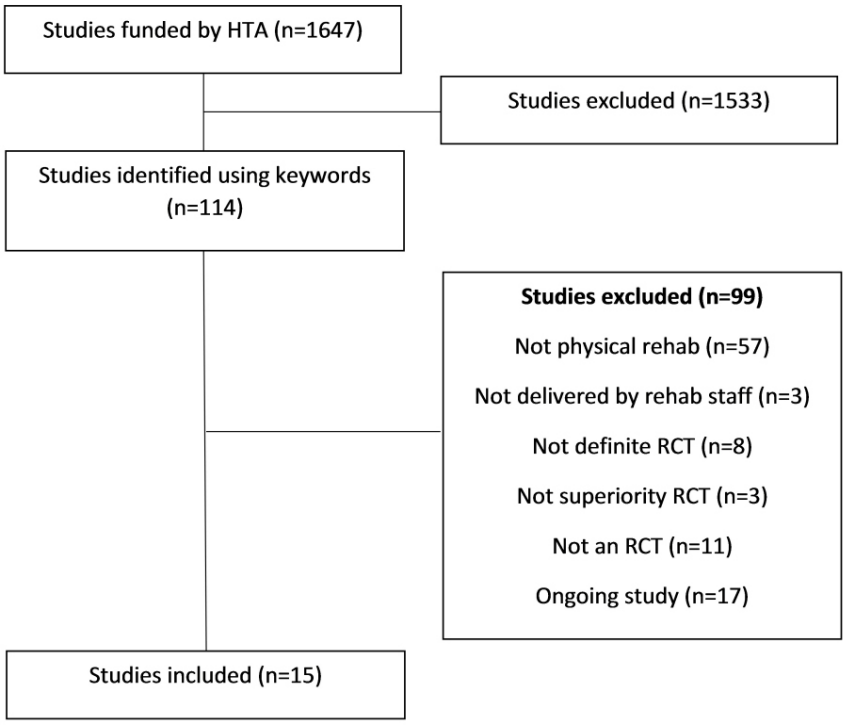


Figure 1 Study selection

Figure 1 Study selection

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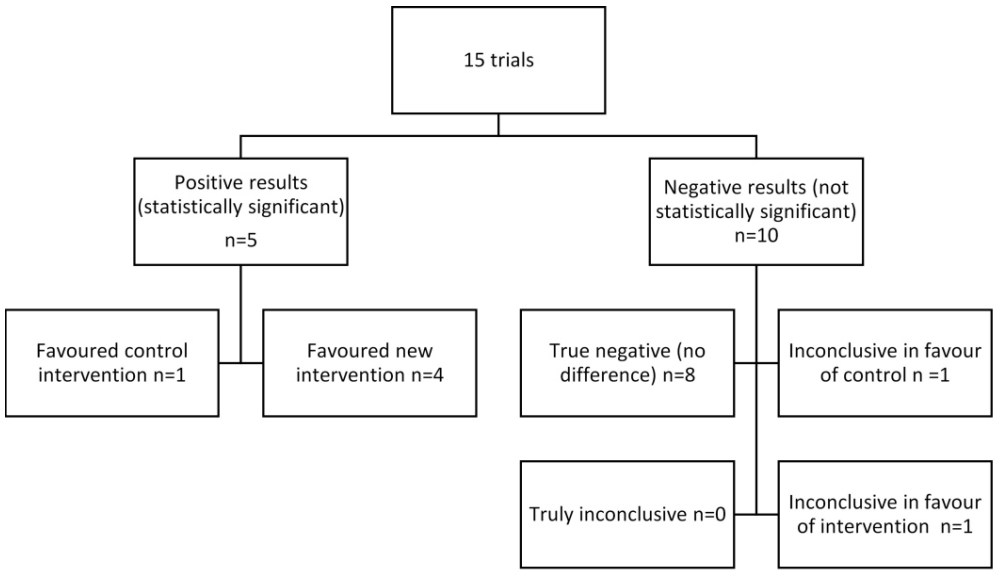


Figure 2 Classification of primary outcome

Figure 2 Classification of Primary Outcome

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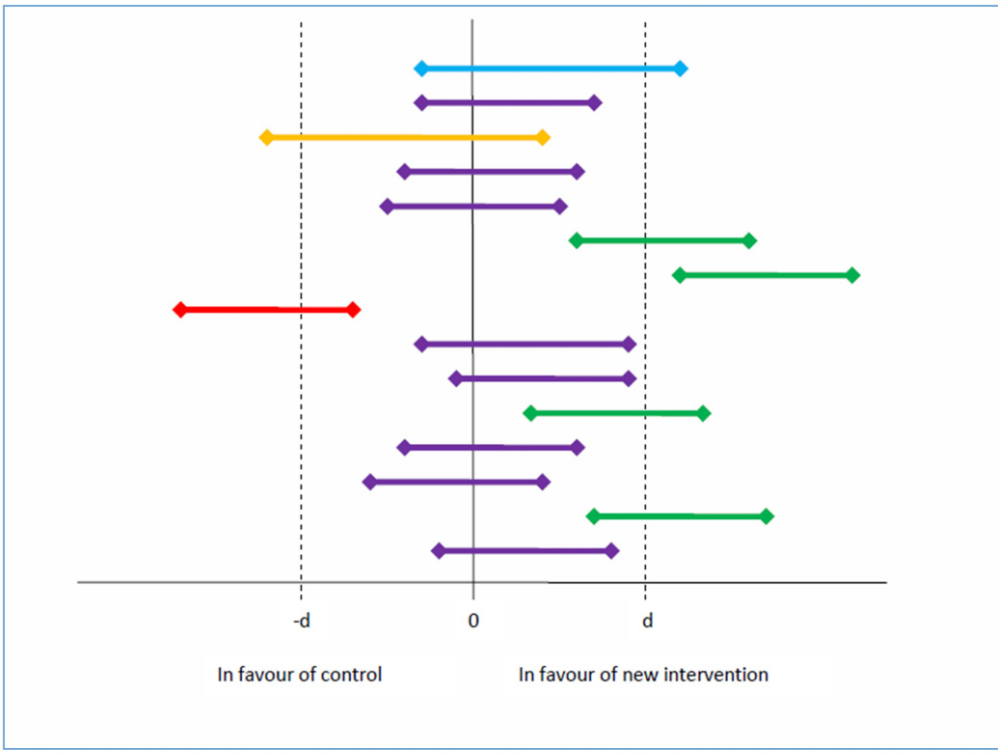


Figure 3 Treatment success of included trials based on 95% Confidence Interval and Minimal Clinically Important Difference from trial sample size calculation (d)

Key: *Green = statistically significantly in favour of intervention; Red = statistically significantly in favour of control; Blue = Inconclusive in favour of intervention; Yellow = Inconclusive in favour of control; Purple = True negative (no difference)*

Figure 3 Treatment success of included trials based on 95% Confidence Interval and Minimal Clinically Important Difference from trial sample size calculation (d)

87x89mm (300 x 300 DPI)